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BRITISH MEDICAL JOURNAL

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PROGRESS IN THE UNDERSTANDING AND TREATMENT OF DIABETES MELLITUS*

BY

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The importance of therapy, day in and day out, for diabetes mellitus with its disabling complications is emphasized by the fact that the disease affects about 1% of the population—indeed, recent American studies aimed to detect the true incidence in the U.S.A. suggest that it may be 2–3%. The present paper is a rather parochial review, its purpose being to consider the therapy of diabetes in relation to current investigations in this field at Guy's Hospital, and the development of some new drugs. The discussion is largely confined to our ideas about the control of diabetes: our studies on complications (Fry, Trounce, and Cook, 1959; Thompson, Butterfield, and Fry, 1960) and our thoughts about treating them have been reported elsewhere (Butterfield, 1961).

Control of Diabetes: Physiological Considerations

Although not necessarily correct, it is customary and convenient to control diabetes by assessing the abnormalities of sugar metabolism rather than those of fat or protein metabolism. Recent investigations with colleagues have provided us with some new ideas about the mechanism of hyperglycaemia and glycosuria.

By studying the forearm tissues in normal and diabetic subjects, we showed (Butterfield and Holling, 1959), contrary to expectations in some quarters—for example, Somogyi, (1949)—that negative arteriovenous glucose differences occur and that the peripheral tissues have a glucose threshold which must be exceeded by the blood-glucose level if glucose is to shift from the blood into the tissues, (see Fig. 1). In normal fasting subjects this threshold was 70–90 mg./100 ml. and the fasting blood sugar approximated very closely to it, so that, under those circumstances, the uptake of glucose by the tissues was negligible. (Mean of six subjects, 0.075 (S.D. ± 0.11) mg./100 ml. forearm tissue/min.) In fasting diabetic subjects the tissue glucose threshold was very much higher, and so was the systemic blood sugar. Again, in stable or severely diabetic subjects there was negligible or even negative glucose uptake in fasting conditions (−0.13 to +0.04 mg./100 ml. forearm tissue/min.). (Fig. 2 exemplifies results in elderly diabetics.) If the threshold in the peripheral tissues exceeded the renal threshold (usually about 180 mg./100 ml.), glycosuria occurred. We have also observed that subcutaneous or intravenous insulin lowers the glucose threshold of the peripheral tissues (Butterfield, Fry, and Holling, 1958) in most subjects. Thus in the elderly diabetic (Fig. 2) the fasting threshold was 286 mg./100 ml. of blood, and

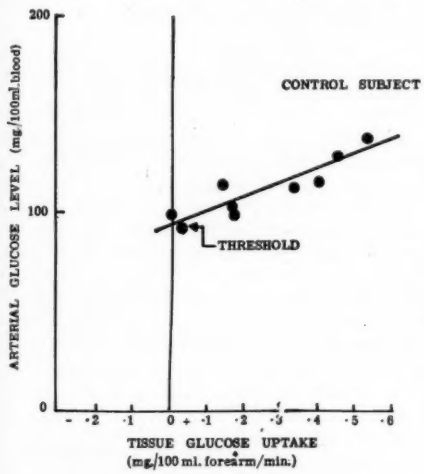


FIG. 1

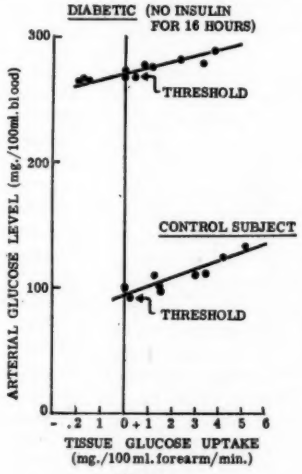


FIG. 2

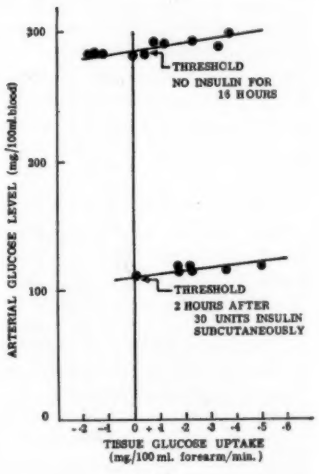


FIG. 3

FIG. 1.—Relationship between arterial glucose level and tissue glucose uptake in a normal subject, showing the tissue glucose threshold. FIG. 2.—Relationship between arterial glucose level and tissue glucose uptake in a normal subject (below) and in an elderly diabetic (above). Note the elevated tissue glucose threshold in the diabetic subject. FIG. 3.—Reduction of tissue glucose threshold in the elderly diabetic by a subcutaneous injection of insulin (30 units). (From Butterfield *et al.*, 1958.)

*Based on a communication to the Section of Medicine at the Annual Meeting of the British Medical Association, Torquay, 1960.

two hours after subcutaneous insulin the threshold had fallen to 110 mg./100 ml. (Fig. 3). Clearly insulin had reduced the tissue glucose threshold, with a consequent fall of the systemic blood level below the renal threshold and disappearance of glycosuria.

When we followed the local effect of small doses of intra-arterial insulin on the tissue glucose threshold of insulin-sensitive subjects we found that it exerted its action very quickly, measurable changes of uptake being detectable within five minutes (Hardwick, Butterfield, Fry, and Briggs, 1959), rising to peak values of over 1 mg./100 ml. forearm/min. by 15 minutes (Fig. 4). Insulin given intravenously to exert a systemic effect produces a fall in blood sugar of similar time response.

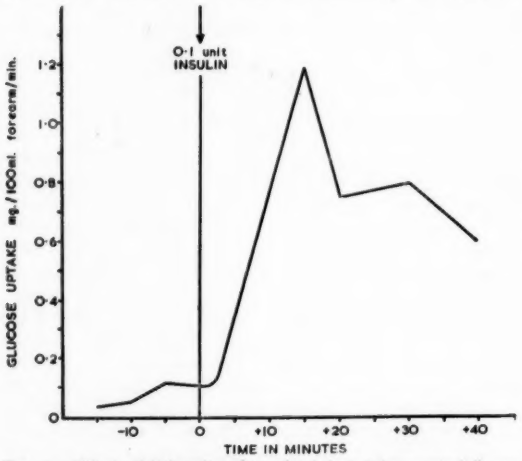


FIG. 4.—Effect of 0.1 units of insulin injected intra-arterially on the local tissue glucose uptake in an insulin-sensitive subject with normal carbohydrate metabolism. (From Hardwick *et al.*, 1959.)

All these findings suggest that the glucose threshold of the peripheral tissues is an important factor controlling the fasting blood sugar level.

Our studies have also shown that when glucose was taken by mouth it moved into the tissues. Thus, in lean normal subjects, of the 50 g. administered in the standard glucose - tolerance test, it may be calculated that 35 g. found its way into the cells of the peripheral tissues. By contrast, in elderly diabetics some 15 g., and in severe insulin - dependent cases only about 1 g., of the original dose enters the cells of the peripheral tissues (Butterfield and Whichelow, unpublished observations). The tissue glucose threshold rose under these circumstances, but in all normal subjects studied it reverted to normal values within 1½ to 2½ hours, whereas in diabetic subjects the abnormally high threshold of the fasting state rose to even higher values and stayed elevated, suggesting that there was insufficient insulin available for homoeostasis (Fig. 5). From these findings, and from the overnight rise of tissue glucose threshold level observed in untreated diabetics, we can deduce that, as glucose finds its way into the tissues, the insulin effect is exhausted.

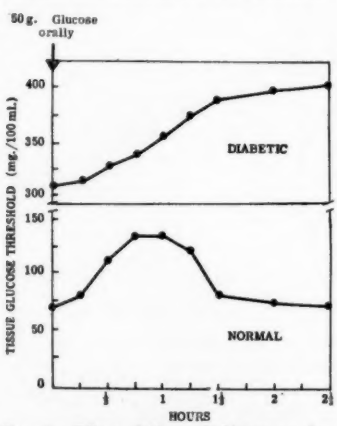


FIG. 5.—Effect of 50 g. of glucose on the tissue glucose threshold in a normal subject (below) and in an insulin-dependent diabetic (above).

All the foregoing results are in harmony with the general hypothesis that insulin acts by increasing cell permeability to glucose, activating a transport system for glucose in the cell membrane. Furthermore, these studies in man, indicating tissue thresholds, suggest an amplification of this view: the effect of insulin on the systemic blood sugar may be due to an increase in the proportion of cells in the peripheral tissues acting as glucose acceptors. I stipulate proportion because effects have been observed under circumstances where the number of molecules of insulin fixed appears to be smaller than the number of cells in the forearm tissues under study. These findings have therefore brought us to regard the body's glucose metabolism in a much more anatomical way—we conceive that different tissues or organs may have different thresholds for glucose, the systemic blood sugar apparently following the peripheral tissue threshold very closely. When the peripheral glucose threshold in diabetes rises above the renal threshold, so that glucose is detectable in the urine, its value is roughly double that which obtains in normal fasting subjects. Thus when we control diabetics by urine-testing, their glucose metabolism may still be abnormal, even though the urine tests for sugar are all negative. The question at present under consideration is whether the brain has a glucose threshold, and, if so, whether it is affected by insulin and whether the symptoms of hypoglycaemia are due to the threshold of the peripheral tissues falling close to or even below the brain threshold.

Clinical Types of Diabetes

Young Diabetics

Elevated glucose thresholds of peripheral tissues may arise owing to inadequate production of insulin. It is generally believed that diabetes which starts during childhood and adolescence—growth-onset diabetes—is associated with an absolute deficiency of, and an inability to produce, insulin. In acromegaly associated with the overproduction of growth hormone in adult life we find that intra-arterial insulin is ineffective in lowering the glucose threshold of the peripheral tissues (Hardwick *et al.*, 1959) (Fig. 6). This seems to be due to failure of insulin to reach the tissues and exert its usual effect there (Briggs, Butterfield, Garratt, Pearson, and Whichelow, 1960). Could the growth hormone present during child-

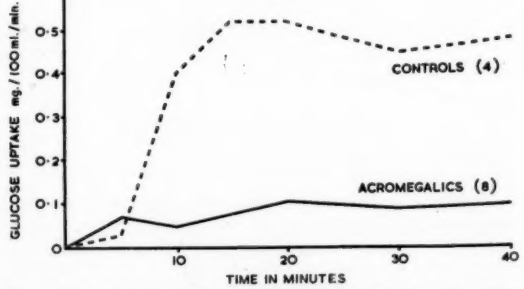


FIG. 6.—Impaired response to intra-arterial insulin, 0.1 units, observed in acromegaly. (From Hardwick *et al.*, 1959.)

hood or adolescence act in a like manner, thereby taxing the β-cells and contributing to their eventual complete exhaustion, thus accounting for the absolute insulin deficiency observed in such cases both during life and in the pancreas at necropsy? Obviously this possibility deserves investigation, particularly in view of the recent evidence that in the early stages of their disease juvenile diabetics have large quantities of insulin in their blood (Steinke, Taylor, and Renold, 1961).

Meanwhile it is important to appreciate that such diabetics, whose disease began during growth, represent but a small fraction, perhaps a sixth, of the cases attending diabetic clinics. Their condition approximates to the concepts of diabetes based on laboratory studies of experimental diabetes produced in animals after pancreatectomy. More recently a new form of experimental diabetes has been produced by workers at Guy's Hospital. Stemming from his interest in insulin assay, recently reviewed (Vallance-Owen and Wright, 1960), my colleague Dr. P. H. Wright, of the department of chemical pathology, in collaboration with Dr. R. T. Grant and Mr. J. Armin (Armin, Grant, and Wright, 1960), has produced a diabetic state by the infusion of insulin antiserum, prepared by injecting bovine insulin into guinea-pigs, as described by Moloney and Coval (1955). The full potential of this new and specific method of blocking insulin action *in vivo* remains to be determined; its great advantage is that one knows the exact time of onset of insulin deficiency in the unanaesthetized, conscious animal.

Patients in whom the onset of diabetes occurred during growth invariably need insulin therapy, for in its absence the glucose threshold of the peripheral tissues rises higher and higher. So long as carbohydrate intake and gluconeogenesis in the liver can keep pace with this and glycosuria, the circulating glucose level will rise, and glucose will compete with other metabolic substances. But if the threshold rises so high that the cells are starved of glucose, the body must rely more and more upon fat mobilized from adipose tissue. This uncontrolled fat metabolism leads to acetonuria.

Older Diabetics

Diabetes is much more prevalent in elderly patients. They represent about 75% of those attending most diabetic clinics—and the proportion is increasing as more and more cases are detected by conscientious practitioners and at detection drives. They rarely have an acute onset of symptoms attributed to glycosuria—dehydration, loss of weight, or diabetic coma. The disease is insidious—indeed, the patient not infrequently presents with symptoms attributable to the complications of diabetes, or has asymptomatic glycosuria found at examination for an insurance policy. In these cases insulin can be found in the circulating blood, and at necropsy in the pancreas. Furthermore, these patients are not prone to develop acetonuria, and the disease can often be controlled simply by dietary restriction; presumably insulin production can keep pace with the slow utilization of insulin accompanying low glucose uptake by the tissues.

However, we are still grossly ignorant of the cause of such inadequate insulin secretion or defective action. Regarding inadequate secretion, one wonders if the β-cells, too, have a glucose threshold which must be exceeded before glucose enters them to act as a stimulus for insulin secretion. Elevation of the β-cell glucose threshold, as part of a generalized process independent of insulin itself, would account for the elevation of blood sugar in these cases, by automatically gearing the release of insulin from the β-cells to a higher level of circulating blood sugar. In regard to defective action, the possibility exists that other cases may have impaired insulin fixation (Yalow and Berson, 1960).

Therapeutic Principles

Current trends of therapeutics for diabetes may be considered in relation to the foregoing information. Table I summarizes the clinical indications for selecting the therapeutic procedure available to-day that is likely to be best.

TABLE I.—*Selection of Therapy for Diabetes*

Presentation	
Diabetic coma or precoma	Insulin—urgent
Glycosuria and acetonuria	Insulin—at least at first—and diet
Glycosuria alone	Diet—especially if patient overweight or diet + oral antidiabetics or diet + insulin

Education of Patients.—Recent studies have indicated that the public is appallingly ignorant about diabetes (Reid, 1960). A prerequisite for proper and sustained control is an understanding of the disease by the patient and his family. This is especially true in severe cases. However, not many patients can grasp the intricacies of glucose assimilation by cells, insulin requirements, or how insulin deficiency causes hyperglycaemia and glycosuria which can be counteracted either by encouraging the β-cells to secrete insulin or by replacement injections. But most of them can grasp the idea that the blood sugar is like water in a wash-basin: add more, and it runs out of the overflow into the cells. Unfortunately the overflow silts up unless there is enough insulin. If it silts up, the level rises and the basin overflows. In the same way, glucose spills over into the urine, where it can be detected by testing. At Guy's Hospital we are looking into visual aids to engender this sort of understanding,

Urine-testing.—In the control of diabetes to-day glycosuria can be assessed without the paraphernalia of spirit-lamps and spurting test-tubes. Simpler methods have been developed involving the use of tablets which generate their own heat on dissolving. It is now reasonable to expect a conscientious patient to perform up to four urine tests for sugar each day, even at work, and record the results in a suitable book for inspection by the doctor at each visit. This has become a basis for assessing and controlling patients in most diabetic clinics.

Diet.—From the previous remarks it is clear that regular dietary control must be the central theme of therapy. In most elderly, obese cases it is the safest and best treatment, often the only treatment, required in the early stages of the disease. The insulin action, inadequate for high carbohydrate intakes, can cope with 80–100 g. a day, and keep the fasting blood sugar under control, to 120 mg./100 ml. of blood or less. Furthermore, glucose tolerance may be improved after effective dieting. It is the general experience that satisfactory gradual reduction of weight in such mild diabetics can be achieved by diets of 1,500–2,000 calories a day, with exercise. This quickly eradicates their glycosuria without resort to any other treatment: the problem in such cases is usually to maintain the initial good intentions of the patients about dieting. However, weight-reducing diets cannot be recommended for thin patients, growing children, or those of any age with severe insulin deficiencies manifest by persistent acetonuria in addition to glycosuria. In such cases it is important to ensure

that there is a suitable intake of carbohydrate for disposal into the tissues each day by insulin or oral antidiabetic drugs (see below.) Clearly, the patient receiving insulin injections risks hypoglycaemia if he eats too little, and hyperglycaemia if he overeats. Adult diabetics who require insulin are maintained on 150–200 calories of carbohydrate a day, with a total daily calorie intake of 1,500–2,500, or more, depending on weight and on physical activity. The latter demands more calories without a proportional increase of insulin dosage.

Insulin

Replacement therapy is imperative in those diabetics whose resources for insulin production are inadequate to maintain reasonable tissue glucose thresholds when they are dieting, or after an overnight fast. These circumstances apply continuously to almost all "growth-onset" cases, but may also arise intermittently in elderly diet-controlled patients in the course of intercurrent infections, illnesses, injuries, or operations. As explained earlier, insulin is indicated if the patient shows persistent acetonuria; its injection in the soluble form by the intravenous route is obviously urgent in the presence of impending diabetic acidosis or coma. Both of these metabolic disturbances, with their attendant clinical features of polyuria, polydypsia, dehydration, acetone-tainted breath, and clouded consciousness, must be regarded as dangerous enough to warrant early transference of the patient to a hospital where pathological laboratory services are available in order to ensure adequate replacement of the lost water and electrolytes as well as to control the blood glucose. The notion that diabetic acidosis could be adequately controlled by feeding fructose—a hexose which enters cells independently of insulin—has not been supported by the studies of Nabarro, Beck, and Stowers (1955).

Over the past 10 years various laboratories and pharmaceutical companies, especially in Denmark, have explored new possibilities for compounding insulin for routine use so that the rate of absorption from the injection site will permit adequate control of the blood sugar over the whole 24 hours. The main purpose has been to secure control overnight, with a view to suppressing diabetic complications. Insulin in the crystalline form is now available, and by grading the crystal size, and thus the surface available for absorption into the body fluids, the effect from a single injection can be extended to run through 24 hours. It has been our experience that larger dosages of these long-acting insulins are required than with two or three injections of soluble insulin, and this must be borne in mind when changing over to such preparations.

Although insulin therapy is universally accepted, we should not overlook the inadequacies of this form of treatment. Commercial insulins are prepared from beef pancreases, and the injections therefore contain a foreign protein-beef insulin, which differs slightly from human insulin, and traces of other animal proteins. A survey of Guy's Hospital patients by Robinson, Langman, and Banfield (1961) revealed antibodies to animal insulin in the blood of very few patients. Occasionally tissue allergies to the animal proteins are shown by local reactions at the site of injections.

Our ignorance about the rate of absorption of insulin injected into different sites is being dispelled. My colleague Dr. C. L. Joiner, using I-131-labelled (soluble) insulin, prepared as described by Pearson (1959), has shown that absorption from subcutaneous injections is faster in the arms (half-period: females 55 minutes, males 67 minutes) than in the thighs (females 99 minutes, males 123 minutes) in normal subjects and somewhat longer in patients (Joiner, 1959). Although exercise had no effect on the absorption rates, more studies are projected to discover the effects of variations of lymph or subcutaneous circulation with alterations of skin and environmental temperatures.

It should also be noted that the endogenous insulin passes, possibly intermittently, into the portal circulation. There is recent evidence that intraportal infusions of small doses of insulin reduce hepatic glucose output in dogs with portocaval shunts but that larger doses do not (Madison, Combes, Adams, and Strickland, 1960). These results become intelligible if one assumes that the smaller doses have a predominant effect on the organ first perfused—the liver—whereas the larger doses also lower the threshold of the peripheral tissues, masking any liver action by reducing the systemic blood-sugar level and stimulating the release of adrenalin (Armin and Grant, 1959.) Such an interpretation may help resolve the confusion about the role of insulin in hepatic glucose metabolism existing between workers in different laboratories using various techniques and a variety of insulin doses and infusions. This is exemplified by the papers at a recent symposium in New York. Mahler, Shoemaker, and Ashmore (1959) found no insulin effect after a single injection of 0.2 unit/kg. intravenously in dogs; de Bodo and colleagues (1959), using intravenous infusions of 0.003–0.006 unit/kg./min., followed by C-14-glucose dilution, and deduced a "restraining" effect on glucose release from the liver, though Wrenshall and Hetenyi (1959) questioned the validity of this technique.

Again, at another meeting in London, de Duve (1960) reported hepatic action of insulin, based on rat-liver slices incubated with a medium containing 1 unit/ml., Tarding and Schambye (1960), using intravenous infusions of 0.02–0.12 unit/kg./hour in dogs, were doubtful if hepatic glucose output was altered; whereas Levine (1960), who has used up to 20 units/kg. in rats, was persuaded that insulin had no effect on the liver. Cori (1960) summarized with the words: "The amount of work on the action of insulin on the liver is large indeed, but it seems we need many more experiments before this problem is finally settled." In settling it, the effects of the insulin dosage, particularly through its route of administration and speed, upon the peripheral threshold must be borne in mind if any hepatic action is to be recognized (Madison, Unger, and Rencz, 1960). Meanwhile, so long as we remain uncertain of the action, in man, of insulin on hepatic metabolism or of the liver on insulin metabolism, we must consider the possibility that the non-physiological—that is, non-portal—route of absorption after insulin injections causes too much active insulin to be presented to the arteries. If arterial tissue has a glucose threshold the accumulation of deposits of fat in the arterial wall may be a reflection of periods when too much insulin was available in the circulating blood.

Oral Antidiabetic Compounds

Investigations in the field of oral diabetic compounds have brought important new developments in the treatment of diabetes. While many of the adult-onset non-ketotic diabetics, notably obese patients, can be controlled adequately by dieting alone, others require additional regulation, which for many years was achieved by insulin injections. It is for these latter that the quest for oral therapy seems to be successful.

The search is not new. Müller (1877) reported that large oral doses of salicylates reduced the blood sugar, and this was rediscovered by Reid, MacDougall, and Andrews (1957). During the first world war, Watanabe (1918) and others reported that biguanidines were effective hypoglycaemia agents and "synthalin" A and B were subsequently prepared and tested. Unfortunately they produced fatal hypoglycaemia and liver damage, and their use was soon set aside in favour of the newly discovered hormone insulin when it became available after 1921. During the second world war Loubatières (1944), working in Montpellier, investigated the hypoglycaemic effects of a sulphonamide, I.P.T.D. (2(*p*-aminobenzenesulphonamido) - 5 - *iso*propyl - thiadiazole) and concluded that its action must be directly on the β-cells, since it was ineffective both in pancreatectomized animals and in insulin-dependent, ketotic, growth-onset diabetics.

This discovery was taken up after the war, especially by the German laboratories, where over 300 compounds with hypoglycaemic properties were synthesized. Four of these have been subjected to clinical trial. The first was carbutamide (BZ 55) (*N*-sulphanilyl-*N*-butyl-carbamide). The next compound to be tried, tolbutamide ("rastinon"), enjoys a remarkable pharmaceutical record to date: it has been reported that over a million patients are taking it at present. Chlorpropamide ("diabinese"), a more potent compound with a longer action, has also been marketed: despite animal toxity tests suggesting that high doses might be nephrotoxic, it seems safe. More recently metahexamide, another long-acting compound, was withdrawn owing to a 2% incidence of jaundice in extensive clinical trials. Other long-acting compounds are currently under study.

The success of these compounds reopened the possibility of oral therapy for diabetes, and it was not surprising that the guanidines were re-examined, since two, chlorhexidine ("hibitane"), used for its bactericidal action in the cleaning of wounds and burns, and an antimalarial drug, proguanil hydrochloride ("paludrine"), had been used extensively without toxic manifestations. At the moment two alternative hypoglycaemic guanides are undergoing trial and are available—phenformin (D.B.I.; (phenethylbiguanide) and metformin hydrochloride ("glucophage"; methylbiguanidine). However, although these compounds are relatively free from serious side-effects, a proportion of the patients receiving them show loss of appetite, nausea, and vomiting, and may develop unexplained acetonuria, so that they are not recommended yet for general use.

The chemical interrelationships between the various oral antidiabetic compounds have recently been reviewed by Mahler (1960): the present status of the compounds in use and undergoing trial is set out in Table II.

Mechanism of Action of Oral Antidiabetic Compounds

Experience with the synthalins, suggesting that hypoglycaemia was due to some toxic action on the liver, dictated a cautious approach to oral preparations, and some knowledge about the mechanism of action of the new oral antidiabetic compounds was demanded before the profession would use them. There was at first scepticism, which we shared, of Loubatières's views about stimulation of insulin release, despite the supporting evidence from animal experiments in which Creuzfeldt and Finter (1956) described degranulation of β-cells and from Pfeiffer and colleagues (1959), who reported elevation of plasma insulin levels in calves after sulphonylurea administration.

However, we have been much less concerned about using tolbutamide since we demonstrated in man (Butterfield *et al.*, 1958) that a few days' therapy reduces the glucose threshold of the peripheral tissues in a way which is indistinguishable from the action of insulin (see Fig. 7). We attribute this to stimulation of insulin secretion, as we have been unable to show any direct action of tolbutamide itself or other sulphonylureas on muscle glucose metabolism when given intra-arterially, either as a single dose or as a continuous infusion. Furthermore, Vallance-Owen, Joplin, and Fraser (1959) have since reported an increase of plasma-insulin-like activity hours after oral tolbutamide. There is therefore evidence in animals of β-cell stimulation, and in man of the appearance of insulin in the blood and of its action on the peripheral tissues, after tolbutamide.

TABLE II.—*Oral Antidiabetic Compounds*

	Found Unsatisfactory	In Use	On Trial
Salicylates (Müller, 1877)	Sodium salicylate, etc.	—	Orthocresotinate
Guanides (Watanabe, 1918)	Synthalin A and B	Phenformin	Metformin
Sulphonyl derivatives (Janbon *et al.*, 1942)	I.P.T.D. Carbutamide Metahexamide	Tolbutamide Chlorpropamide	Various analogues

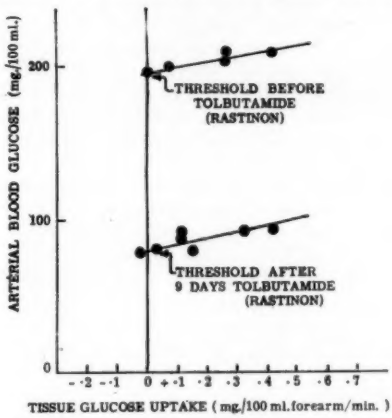

ARTERIAL BLOOD GLUCOSE (mg./100 ml.)
200
100
0
THRESHOLD BEFORE TOLBUTAMIDE (RASTINON)
THRESHOLD AFTER 9 DAYS TOLBUTAMIDE (RASTINON)
-·2 -·1 0 +·1 ·2 ·3 ·4 ·5 ·6 ·7
TISSUE GLUCOSE UPTAKE (mg./100 ml. forearm/min.)

FIG. 7.—Tissue glucose threshold of an elderly diabetic before and after nine days' oral antidiabetic therapy. (From Butterfield *et al.*, 1958.)

Phenformin has a similar threshold-lowering effect, but is not hypoglycaemic in normal subjects and is stated to be hypoglycaemic in pancreatectomized animals maintained on insulin. Its action is therefore presumably different and independent of stimulation of insulin secretion. Our studies show that it does not increase muscle glucose uptake when injected intra-arterially in dose-ranges used clinically. We have recently accumulated evidence from several types of investigation that phenformin enhances the effect of circulating insulin (Butterfield, Fry, and Whichelow, 1961), which we could not demonstrate for sulphonylureas (Butterfield, Camp, Hardwick, and Holling, 1957).

Selection of Cases for Oral Antibiotics

The foregoing explanation about modes of action of oral antidiabetic compounds may now be dovetailed into our empirical clinical knowledge of the type of case that can be selected for their use.

Sulphonylureas

It has been pointed out by German investigators who pioneered the clinical trials of sulphonylureas that the prospects of successful therapy increased with the age of the patient—being very good over the age of 40—and that they were related to a less extent to the duration of the disease, being best if the diabetes was of less than five years' duration (Mohnike and Stötter, 1956). The idea behind the second principle was that after prolonged hyperglycaemia the islets became exhausted. In contrast, severely ketotic, intensely hyperglycaemic, or young diabetics are not amenable to control with the sulphonylureas. The two most widely used sulphonylureas are tolbutamide and chlorpropamide. Relevant information about both these drugs is presented in Table III.

Our general views about the steps to be taken when trying sulphonylurea therapy have been reported previously (Butterfield, Fry, Hardwick, and Holling, 1957). In those patients who are not on insulin—after suitable baseline observations of glycosuria (see above), including a check for renal glycosuria—the sulphonylureas—for example, tolbutamide—may be started 1 g. t.d.s. for one day, then 1 g. b.d., tapering off as and when the patient shows a response. As we pointed out, while this is usually effective after two to four days, it may take a week or even longer; we have also often noted a brief response at the second to fourth day in patients who have subsequently failed to maintain it.

If the patient is receiving less than 20 units of insulin a day it is possible to convert to tolbutamide without admission to hospital. We halve the insulin dosage during the first week as the oral compound begins to take over control.

If the patient requires over 20 units of insulin a day it is wise to try a conversion to tolbutamide in hospital: a successful conversion is very unusual in cases needing over 80 units of insulin a day. Therapy with a combination of tolbutamide and insulin has been tried but has little to recommend it.

Tolbutamide certainly seems to be the safest drug of this group, but needs frequent administration—up to three times a day. If control is tried with the other sulphonylureas, the possibility of the following side-effects must be borne in mind. With carbutamide, cases of agranulocytosis and liver damage have been reported. With chlorpropamide, also given once a day, the main difficulty is balancing between failure to maintain adequate control overnight and hypoglycaemia if effects accumulate. The main disadvantage of all sulphonylureas is that a proportion of cases fail to maintain their control (secondary failure). The cause of this loss of sensitivity is being investigated intensively in many centres.

Guanides

Although not yet in general use, a note may be added about the guanides. Phenformin is now available, and relevant information about it is given in Table III. Cases selected for trial embrace not only the type suitable for the sulphonylureas but also those whose control on insulin is adequate. In the latter cases it may be possible to "smooth" the effect of insulin and improve control. Guanides may therefore be suitable for younger patients and patients who show ketosis. Another difference compared with the sulphonylureas is that treatment is started at low doses and increased very slowly. With cases on diet alone this may be done on an out-patient basis, but for those on insulin admission to hospital is mandatory. The rate of response may be slower than that found with tolbutamide, but, in our experience, good results have been unusual in cases on high doses of insulin: our findings are comparable to those of Krall, White, and Badley (1958).

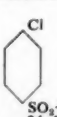
Although there seem to be few serious toxic effects with phenformin, there are unpleasant side-actions. About a third of all patients complain of nausea and vomiting, and we have some laboratory evidence that this is associated, sometimes at least, with non-absorption of glucose. Some patients have reported that their exercise tolerance is diminished by "fatigue," which may be due to accumulation of lactic acid (Walker, Linton, and Thomson, 1960). It is important to point out that acetonuria in the absence of hyperglycaemia may be observed in some patients on phenformin. Acetonuria is usually an indication for increasing the dose of antidiabetic drugs, such as insulin, but treating acetonuria in the absence of glycosuria may lead to serious complications with phenformin (Walker and Linton, 1959), and a closer analysis is required. Pomeranze (1960) has suggested that the acetonuria is due to non-absorption of food, like starvation ketosis. However, we have observed it in many patients who are gaining weight, and its true basis remains to be elucidated.

Perspective.—It may help to bring the various therapies into perspective by quoting current experience in diabetic clinics. All patients on dietary restriction are encouraged to check their urine for glycosuria and to record the results. About half the cases need insulin in addition to diet, and about a fifth use the sulphonylureas, while a much smaller fraction (1–2%) take guanides or mixed oral and insulin therapy.

Conclusions

Diabetes is a long-drawn-out disease, and it remains to be seen whether the oral antidiabetic drugs will maintain satisfactory control year after year. The secondary failures encountered after a few months may

TABLE III.—*Comparison of Three Oral Antidiabetic Compounds Currently in Use*

	Tolbutamide	Chlorpropamide	Phenformin
Formula	$SO_2 \cdot NH \cdot CO \cdot NH \cdot C_4H_9$	 $SO_2 \cdot NH \cdot CO \cdot NH \cdot C_3H_7$	$C_2H_4 \cdot NH \cdot C(=NH) \cdot NH \cdot C(=NH) \cdot NH_2$
"Half-life"	4–8 hours	24–48 hours	6–8 hours
Dose rate	0·5–1·5 g./day	125–500 mg./day	50–200 mg./day
Cost (Guy's cases)	About 5½d./day	About 5d./day	About 1s./day
Complications	Very rare	Rare	(Nausea)
Remarks	Probably the safest, but must be given several times/day	Probably the cheapest but not necessarily the safest	May have applications in some insulin-deficient cases

not so much be sporadic cases as those which show relatively early failure; a larger proportion may deteriorate later on. It has been suggested that the hyperglycaemia of secondary failure may be treated with salicylates or guanides, but the long-term success of these measures is unproved.

More important, though, is the question of diabetic complications, for we must appreciate that the real problem now hinges much more on the development of these than the question of controlling the blood-sugar level. We should be concerned with the prevention and amelioration of disability from vascular disease of the eye, lower limbs, and kidney, and the neuropathies of diabetes. In general practice much can be done to alleviate suffering by the early detection of diabetes by testing the urine with the sensitive glucose-specific tests available, thereby bringing therapy to the patient and getting the blood-sugar level under early control, which offers the best hopes of reducing the incidence and severity of complications. The ultimate value of any diabetic therapy, be it oral or by injection, must be judged by the progress of diabetic complications, and answers in these terms rather than glycosuria must now be sought.

The foregoing has focused attention on the hospital and laboratory view of diabetes, and it seems salutary to conclude by standing up from the bedside and work-bench to take a broader look and to make some more general remarks about the team-work which is needed to deal with diabetes on a national scale. Diabetes offers an excellent example of the wider implications of chronic disease to-day, including the social, medical, public health, and occupational aspects, all of which must be considered. Furthermore, as the expectation of life is extended the proportion of diabetics in the elderly population will increase, so that the problems are likely to become more important in the future. This challenge demands the integration of many types of human activity, and in Table IV I have tried to summarize various responsibilities which must be met if the disease is to be mastered, and have attempted to set these against the groups who, it seems to me, must accept them.

If the medical profession is to play its proper part, it must take the overall responsibility for ensuring that all members of the team really appreciate their job and stick to it. Thus every doctor knows that, in the last analysis, the best dietetic advice is of no avail if the patient secretly consumes sweets—so the good doctor motivates his diabetics, emphasizing in their minds the importance of diet, and indicating that this is the patient's responsibility. Likewise, the relatives may need guidance before they will come forward for tests to detect any other members of the family who have diabetes. And, on general principles, the profession must encourage the pharmaceutical industry to produce the best possible insulin preparations and the safest oral antidiabetic drugs. Finally, we must always be prepared to help the lay organizations—diabetic associations—and the public health authorities to provide group activities for diabetics and in tracing the other latent diabetics in the community. So long as this overall team-work is incomplete, diabetes will undermine the health of the community and produce disability.

TABLE IV.—*Responsibilities In Treatment of Diabetes on National Scale*

The challenge of diabetes must be met by—	
1. The patient	His diet
2. His family	Education about diabetes, urinalysis, personal hygiene, diabetic relatives
3. His doctors	Control therapy—insulin and oral antidiabetic drugs
4. Research worker	Study of diabetes, especially complications
5. Pharmaceutical industry	Safe drugs
6. Lay organizations	Arousing public interest, raising funds, and helping patients
7. In collaboration with public health authorities	Detection of latent diabetics; prevention of disease

Many of the studies referred to above were undertaken at Guy's Hospital. I am indebted to my colleagues for their co-operation and to my laboratory assistants. Some of the investigations were performed during an appointment with, and others aided by grants from, the Medical Research Council, to whom I am grateful for support. Figs. 4 and 6 are printed by courtesy of the Editors of the *Proceedings of the Royal Society of Medicine*, and Figs. 3 and 7 by kind permission of the Editors of *Diabetes*.

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IMMUNOLOGICAL STUDIES WITH CIRCULATING INSULIN

BY

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While the chemical structure of insulin as extracted from the pancreas is now known (Sanger, 1960), our knowledge of the form in which insulin circulates in the blood-stream remains fragmentary. It would be surprising if the changes of physico-chemical environment as a result of passing through the liver, lungs, and endothelial lining of the capillaries did not in some way modify the properties and also the biological effects of insulin. Knowledge of the possible modifications of insulin after it leaves the pancreas is clearly important in our understanding of conditions such as diabetes mellitus. In this communication we describe experiments which suggest that there is an immunological difference between circulating and extracted pancreatic insulin.

Methods and Material

Assay Procedure (Modified from Martin, Renold, and Dagenais, 1958)

Fed male Wistar rats weighing 125–130 g. were killed by cervical fracture and then bled by partial decapitation. The epididymal fat tissue was floated out in Krebs-bicarbonate buffer containing D-glucose (300 mg./100 ml.), at room temperature. The leafy portion of each fat pad was cut longitudinally into six or seven pieces weighing 10–20 mg. each. These were visually grouped for comparability of surface area, pieces from different groups then being used to make up the set of tubes for any particular estimation.

The pieces of fat tissue were placed in 1 ml. of incubating medium, contained in wide-necked glass tubes carrying a side-arm (15 ml. in volume). A large rubber stopper with a central diaphragm closed the mouth of the tube and an all-glass cup of 1.5-ml. capacity was suspended from the under-surface. Smaller gas-tight rubber bungs were inserted into the side-arm.

The system was equilibrated with 5% CO_2 and 95% O_2 at 37° C. for 5–10 minutes and was then sealed off, all subsequent manipulations being made via needles attached to spring-loaded syringes. Finally, 1 ml. of gassed Krebs-bicarbonate buffer at 37° C. containing 0.2 μc ^{14}C-1-glucose was introduced through the side-arm, making a total volume of 2 ml. of incubating medium.

The Krebs buffer or other incubating media were invariably made up to a final glucose concentration of 300 mg./100 ml. and gelatin (200 mg./100 ml.) was added.

The incubation was carried out in a Dubnoff metabolic tank at 37° C. for 120 minutes at 70–80 oscillations per minute. Then 1 ml. of a 1 M solution of hydroxide of "hyamine" (*p*-(diisobutyl-cresoxy-thoxyethyl)dimethyl benzyl ammonium hydroxide) in methanol was placed in the central hanging cup and 0.2 ml. of 1 N H_2SO_4 introduced into the incubating medium. After cooling the bath water to approximately 25° C. the tubes were shaken at 120–130 oscillations per minute for three hours. The hanging cups were then detached, and, after washing the outside thoroughly in water, placed directly into 10 ml. of toluene scintillator (2,5-diphenyloxazole (POP) 4 g. and 1,4-bis-(2-(5-phenyloxazolyl))-benzene (POPOP) 50 mg./l.) contained in low-background glass counting-phials. The hyamine was mixed carefully with the scintillation fluid and the cup removed.

The fat tissue was washed thoroughly, blotted, and dried in a desiccator overnight in pre-weighed tubes. The tissue was then weighed and homogenized into 20 ml. of ethanol: petroleum ether, 3:1. After centrifuging, the supernatant was well shaken with 10 ml. of normal saline and allowed to separate at 4° C. 3-ml. aliquots of the upper layer were placed in pre-weighed counting-phials and the petroleum ether was evaporated with a jet of nitrogen. After removing traces of water by drying overnight in a desiccator, the fat in the phials was weighed and 10 ml. of the liquid scintillator added.

The samples were counted in a Packard "tri-carb" liquid scintillation spectrometer at high-voltage tap 10 (1,365 volts) with lower discriminator bias settings of 10 volts. The proportion of the total counts recorded between 10 and 60 volts serves as a monitor for excessive quenching. The results are expressed as counts per minute per $\sqrt{\text{dry weight}}$ of *tissue* (for CO_2) or *fat* per 120 minutes (c/m/$\sqrt{\text{dw}}$/120 min.).

Preparation of Insulin Extracts.—Extracts of serum and of pancreatic tissue were made according to the method of Jephcott (1931) as modified by Grodsky and Forsham (1960).

Preparation of Insulin Antibody.—Immune guinea-pig serum against ×6 recrystallized insulin (Boots Pure Drug Co. Ltd.) was prepared according to the method of Moloney and Coval (1955) as modified by Wright (1959). In all experiments in which the effect of insulin antibody was assessed control guinea-pig serum was obtained either from normal animals or from animals injected with the inoculum alone (lanolin and Freund's adjuvant). The potency of these antisera naturally varied, but a considerable excess of antibody was always used. All the immune guinea-pig antisera employed in these experiments were shown to antagonize fully the effect of 900–1,000 μU/ml. of crystalline ox insulin at, or at less than, the concentrations used in the serum or serum extract experiments. Most of the immune serum samples had also been shown to produce transient hyperglycaemia when injected into rats and to be capable of agglutinating insulin-coated red blood cells (Robinson and Wright, 1961).

Results

Fat-pad Insulin-assay Procedure's Sensitivity and Precision.—The method appears to be highly sensitive to pancreatic insulin. The Table shows the values obtained for the basal tissue activity (without insulin) and its response to a standard amount of crystalline ox insulin (900–1,000 μU/ml.—that is, 1,800–2,000 μU/tube). This standard insulin dose increases the rate of $^{14}CO_2$ production by tenfold to elevenfold, and the rate of ^{14}C-fat formation (ether-extractable material) by twelvefold to thirteenfold. A smaller number of

observations were made with a very low insulin concentration (8 μU/ml. or 16 μU/tube). These showed a mean rise of 90% over the basal values ($P<0.001$).

Further studies of the dose response relationship of the method are in progress, but the figures reported above suffice for the interpretation of the present experiments.

The measurements are also reasonably precise. For the rate of $^{14}CO_2$ production the coefficient of variation of the 39 basal observations was 31%, and of the 37 observations with the standard insulin concentration 30%. Corresponding values for the rate of ^{14}C-fat formation were 39% basally and 35% with insulin. These figures refer to the results obtained in *all* experiments, although within any one experiment (when only a single animal is used—12–15 tubes) the variability is much less. It will be noted that the variability obtained with rat epididymal fat tissues by our technique compares favourably with rat-diaphragm method of insulin assay (Groen *et al.*, 1952 ; Randle, 1954 ; Vallance-Owen *et al.*, 1955) despite the greater sensitivity.

Effect of Guinea-pig Antiserum on Insulin-like Activity of Crude and Crystalline Extracted Pancreatic Insulin.—First a study was made of the effect on the subsequent fat-pad assay of adding immune guinea-pig serum to the crystalline ox insulin or to other crude insulin preparations obtained by making acid–ethanol extracts of human, ox, and dog pancreas. In all instances the stimulating effect of these various pancreatic insulins on both ^{14}C-fat formation and on $^{14}CO_2$ production was abolished completely by the antiserum when compared with the values obtained after adding control or non-immune guinea-pig sera. Figs. 1 and 2 illustrate this inhibitory effect of insulin antibody on the rate of ^{14}C-fat and $^{14}CO_2$ formation when incubations were made with crystalline ox insulin (Fig. 1) or with crude human or ox insulin (Fig. 2). Preliminary results indicate that this is also true of crude guinea-pig insulin ; yet, in accordance with the work of others (Moloney and Coval, 1955 ; Wright, 1959), none of the immunized guinea-pigs became diabetic.

Effect of Guinea-pig Antiserum on Insulin-like Activity of Whole Serum.—In contrast to the effect on pancreatic insulin preparations, the insulin-like activity found in samples of whole serum obtained postprandially from either normal humans or the cow was found to remain unimpaired when incubations were carried out with immune guinea-pig serum. This was true for both the rate of ^{14}C-fat formation and $^{14}CO_2$ production. In the case of the ox serum experiments a relatively high concentration of guinea-pig antiserum was used ($\frac{1}{4}$), and any question of species difference was obviated because ox insulin had been injected to immunize the guinea-pigs.

Effect of Insulin on Rate of ^{14}C-fat Formation and $^{14}CO_2$ Production from ^{14}C-1-Glucose by Rat Epididymal Fat Tissue

	^{14}C Fat Formation†				$^{14}CO_2$ Production†			
	No. of Obs.	Mean	Coef. Var.*	S.E. of Mean	No. of Obs.	Mean	Coef. Var.*	S.E. of Mean
Basal tissue activity	34	99	39%	6·6%	39	126	31%	4·8%
Insulin 8 μU/ml. buffer	8	187	13%	4·5%	—	—	—	—
Insulin 990–1,000 μU/ml. buffer	31	1,277	35%	6·3%	37	1,344	30%	5·0%

* Coefficient of variation.

† Activity expressed as counts per minute per dry weight *fat* (^{14}C-fat ormation) or tissue ($^{14}CO_2$-production) per 120 minutes.

Effect of Guinea-pig Antiserum on Activity of Serum Extracts.—In order to increase the specificity of the method for the detection of insulin in serum, and in order to reduce the effect of possible substances in the serum which could interfere with the antigen–antibody reaction, postprandial sera from man and from the cow were extracted by the same method employed for the extraction of insulin from the pancreas. When these were incubated with and without antibody, there was again no demonstrable effect of the immune guinea-pig serum on the rate of ^{14}C-fat formation (Fig. 3). $^{14}CO_2$ production was also unaffected.

Effect of Guinea-pig Antiserum on Activity of Serum or Serum Extracts with Added Crystalline Ox Insulin.—To assess further whether there were substances in serum which could interfere with the antibody–antigen reaction, crystalline ox insulin was added to whole or extracted serum and the biological effect measured with and without anti-insulin serum. It was found that the insulin-like activity of whole human serum to which crystalline ox insulin had been added *in vitro* 500 μU/ml.) could be reduced by immune guinea-pig serum to the level produced by serum alone. Similar findings were obtained with serum taken from a newly discovered diabetic patient of the juvenile variety, four hours after a subcutaneous dose of soluble ox insulin—that is, with insulin added *in vivo*. Finally, crystalline ox insulin was added to serum extracts from blood collected from a dog four days after total pancreatectomy, when the

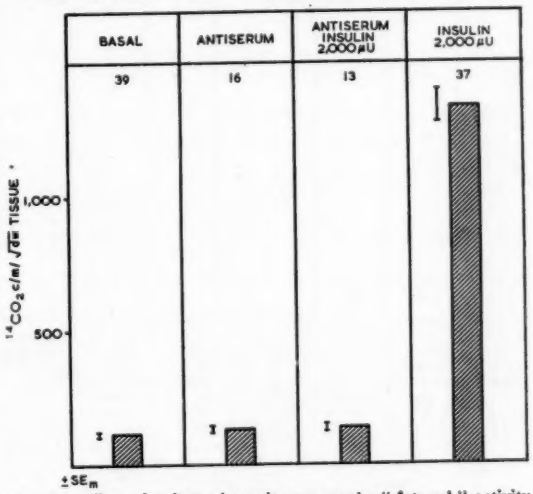

FIG. 1.—Effect of guinea-pig antiserum on the " fat-pad " activity of crystalline ox insulin.

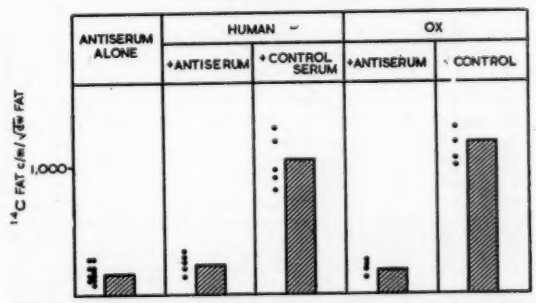

FIG. 2.—Effect of guinea-pig antiserum on the " fat-pad " activity of acid–ethanol extracts of human and ox pancreas. Each dot represents a single estimation.

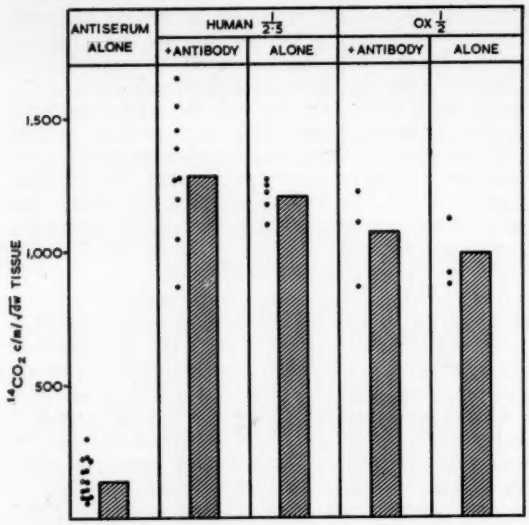

FIG. 3.—Effect of guinea-pig antiserum on the "fat-pad" activity of acid–ethanol extracts of postprandial human and ox serum. Each dot represents a single estimation.

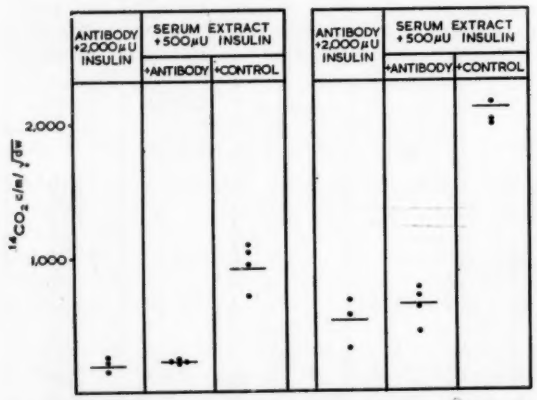

FIG. 4.—Effect of guinea-pig antiserum on the "fat-pad" activity of acid–ethanol extracts of serum with added crystalline ox insulin. Blood was collected four days after total pancreatectomy in a dog Results of two separate experiments.

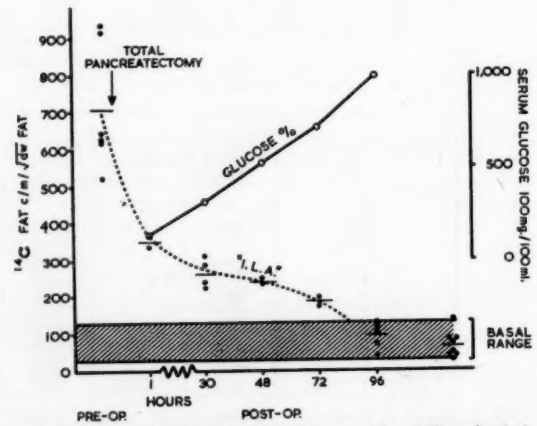

FIG. 5.—Effect of total pancreatectomy on the ability of whole serum to stimulate ^{14}C-fat formation from ^{14}C-1-glucose.

blood-sugar concentration had risen to 997 mg./100 ml., and when the serum alone gave no detectable insulin-like activity as measured by ^{14}C-fat formation. Fig. 4 shows that when crystalline insulin was added in amounts likely to be present physiologically (250 μU/ml.), the insulin-like activity of the serum–insulin mixture could still be abolished by immune guinea-pig serum.

Effect of Total Pancreatectomy on Serum Insulin-like Activity.—Evidence which suggests that the capacity of whole serum to stimulate ^{14}C-fat formation by rat epididymal fat tissue from ^{14}C-1-glucose depends largely upon the presence of insulin was obtained by studying the effect of total pancreatectomy on the insulin-like activity in the dog's serum. Fig. 5 shows that by the fourth post-operative day (when the blood-sugar level had reached 997 mg./100 ml.) the insulin-like activity, as measured by ^{14}C-fat formation, had fallen progressively to within the range of the basal estimations. But, in accordance with the work of Leonards (1959), this was not true of $^{14}CO_2$ production. The mean fourth-day serum activity as measured by this means was 337 c/m/$\sqrt{dw}$ tissue/120 min., nearly three times higher than the mean basal figure for these experiments (119 c/m/$\sqrt{dw}$ tissue/120 min.).

Discussion

Winegrad and Renold (1958) have shown that pancreatic insulin *in vitro* will greatly increase the rate of both $^{14}CO_2$ production and ^{14}C-fat formation from ^{14}C-1-glucose by rat epididymal fat tissue. Our results confirm this and also the insulin sensitivity of the procedure, as Martin *et al.* (1958) have also found, However, whether the stimulating effect of serum or plasma on rat epididymal fat is due wholly, or at least largely, to the presence of circulating insulin is difficult to prove (Leonards, 1959).

Our results with antiserum to ox insulin prepared in the guinea-pig indicate that the insulin-like activity (as measured by both ^{14}C-fat formation and $^{14}CO_2$ production from ^{14}C-1-glucose) of either whole serum or acid–ethanol serum extracts is little, if at all, inhibited by the presence of an insulin antibody in the incubating medium. This result stands in striking contrast to the results reported by Taylor and Randle (1959) using rat hemidiaphragms. They found complete inhibition of serum-insulin-like activity (glucose uptake) when whole ox serum was incubated in the presence of a similarly prepared antiserum to ox insulin. Our results might suggest that the insulin-like activity of post-absorptive serum, whether assayed whole or in acid–ethanol extracts by the rat epididymal fat-assay method, is not due to the presence of circulating insulin; but this is unlikely.

Firstly, the method is highly sensitive to insulin, and all our sera were collected after a carbohydrate meal, when insulin would be expected in the circulating blood and can be detected by immunochemical assay (Grodsky and Forsham, 1960; Yalow and Berson, 1960). Even if relatively small amounts of insulin are present in serum the method should detect it in postprandial blood. Secondly, after total pancreatectomy the dog's serum-insulin-like activity as measured by ^{14}C-fat formation fell to within the range of the basal values; which is strong presumptive evidence that the internal secretion of the pancreas is being measured.

Although antagonism to the effect of insulin on rat-diaphragm muscle has been demonstrated after total pancreatectomy in the cat (Vallance-Owen and Lukens, 1957), this may not apply to adipose tissue. Following the methods of Vallance-Owen *et al.* (1958), C. Lowy, G. Blanchard, and D. Phear (1960, personal communication) have shown that albumin extracts of plasma proteins precipitated by trichloracetic acid do not affect the action of insulin on rat epididymal fat tissue (glucose uptake and $^{14}CO_2$ production.

In confirmation of the work of Leonards (1959) after total pancreatectomy the rate of $^{14}CO_2$ production remains above the basal values, and it is for this reason that the data obtained in the present experiments have been illustrated by the effect on ^{14}C-fat formation. Further work is clearly needed to clarify the nature of this difference. High concentrations of adrenaline, cortisol, and growth hormone will stimulate $^{14}CO_2$ production from ^{14}C-1-glucose, although ^{14}C-fat-formation is either unaffected or depressed (Winegrad *et al.*, 1959; Lynn *et al.*, 1960; Hagen and Ball, 1960; Jeanrenaud and Renold, 1960).

Thirdly, further evidence that the effect of serum on rat epididymal fat tissue is at least largely due to insulin is provided by Owen (1960) and Renold *et al.* (1960), who find that reduced glutathione, which inactivates insulin, will also inactivate the effect of serum on the rate of $^{14}CO_2$ production by rat epididymal fat tissue. Finally, Renold *et al.* (1960) report a twofold to fourfold increase of serum insulin-like activity ($^{14}CO_2$ production from ^{14}C-1-glucose) after intravenous glucose administration.

Thus the activity of serum or serum acid–ethanol extracts on the rat epididymal fat pad is probably largely due to insulin but is little if at all antagonized by insulin antibody. It is possible that there are substances present in serum which interfere with the union of insulin and its antibody, but Moloney and Coval (1955), Arquilla and Stavitsky (1956), and Yalow and Berson (1960) have produced good evidence that at least injected insulin and some endogenous insulin will unite with antiserum to crystalline insulin prepared in the guinea-pig. Furthermore, the stimulating effect of ox serum on the *in vitro* glucose uptake by the rat diaphragm is completely inhibited by immune guinea-pig serum (Taylor and Randle, 1959). Thus lack of union between insulin and its antibody is unlikely as an explanation of our findings. Clearly, therefore, there is a difference, demonstrable immunologically, between insulin extractable from the pancreas and that extractable from the serum of the same animal. This conclusion receives confirmation from the work of Moloney and Coval (1955) and Moloney and Aprile (1959), who have shown that antiserum to crystalline ox insulin prepared in the sheep, rabbit, and horse will inactivate the biological effect (mouse-convulsion procedure) of insulin extracted from the pancreases of these same animals, none of which became diabetic. The nature and physiological significance of this immunological difference is at present being studied.

Summary

Rat epididymal fat tissue has been used *in vitro* for the assay of insulin and insulin-like activity by measuring the rate of production of $^{14}CO_2$ and ^{14}C-labelled fat from ^{14}C-1-glucose.

The stimulating effect of crude pancreatic extracts from various animals on both these parameters of insulin action was completely abolished by an insulin antiserum.

Postprandial serum, whether whole or as an acid–ethanol extract, enhanced both $^{14}CO_2$ production and ^{14}C-fat formation, but this insulin-like activity was not affected by insulin antiserum.

After pancreatectomy in the dog, the stimulating effect of the whole serum on ^{14}C-fat formation was lost, suggesting that this effect of normal serum is due to insulin.

These findings suggest that there is a difference, demonstrable immunologically, between circulating and pancreatic insulin.

We are grateful to Dr. P. H. Wright and Mr. C. Tarrant for much help and for the supply of some guinea-pig antiserum samples; to Messrs. W. J. Dempster and J. Anderson, of the department of experimental surgery at the Postgraduate Medical School of London, for carrying out the animal surgery; to Boots Pure Drug Company for supplies of crystalline insulin free of glucagon; and to the British Insulin Manufacturers and the British Diabetic Association for grants towards this research work.

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A manuscript item recently acquired for the History of Medicine Division of the National Library of Medicine is a ledger into which are pasted some sixty documents covering the service of Dr. Edward B. Dalton (1834–1872) with the U.S. Volunteers from the State of New York during the Civil War. A letter of special interest is dated from Georgetown in October, 1864; it is in an uneducated hand and apparently concerns one of Dr. Dalton's patients. Addressed "dear Friend Abreham Lincon," it reads: "as my husband is in your serviz and is sick and the docter ses that he never will bea no beter . . . if you please send him his discharge as he can do you three times as much good here in the comen election as his influence is greate here and i feal ancies to have him here as i dont want the trater mack [George Brinton McClellan] in the chare . . ." (*National Library of Medicine News*, May, 1961.)

A STUDY OF 183 ROAD DEATHS IN AND AROUND BIRMINGHAM IN 1960

BY

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AND

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This study is of 149 persons who died as the result of road accidents in Birmingham during 1960, and 34 others who died from road accidents outside the city but who were brought to city hospitals and came under the jurisdiction of the city's coroner.

It may be of interest that a further three drivers (all males) of motor cars died from natural causes. One, a taxi-driver aged 61, known to have suffered from cardiac trouble for a considerable time, had a heart attack while driving his taxi, collided with the rear end of a corporation bus, and died from coronary thrombosis. Another, aged 46, when driving his car braked suddenly to avoid hitting a pedestrian on a pedestrian-crossing; his car then collided with a motor-scooter. He left his car to 'phone his wife and was about to light a cigarette when he collapsed and died from coronary thrombosis. The third, aged 60, was driving his car when he lost control and collided with a stationary motor-van, which in turn struck another stationary car; necropsy revealed that death resulted from cerebral haemorrhage caused by hyperpiesia due to natural causes. None of these three accidents resulted in serious injury to any road user.

The material studied includes the coroner's files, made available through the ready co-operation of Mr. G. Billington, the Birmingham coroner, and the necropsy reports of his panel of pathologists. Further details of the objects causing injury and photographs of vehicle damage were collected by members of our group with the co-operation of Mr. E. J. Dodd, the Chief Constable of Birmingham, and his staff. This evidence has been related when possible to our own and other hospital clinical records.

In spite of the increasing number of road deaths, studies of their necropsy pathology are few, and with one exception—that of Eckert *et al.* (1959)—are limited to reports of injuries to special areas of the body. This more general study shows that the severity and multiplicity of injuries in one person cut across all branches of medicine with a superb disdain for the man-made boundaries of the different specialties, presenting the hospital service with a very real challenge to provide appropriate treatment facilities within the time when treatment can be most successful.

Most of the accidents here recorded occurred in a provincial city where the roads are overcrowded, roadside parking commonplace, road turnings frequent, and clear vision around corners exceptional. Cars, lorries, vans, and buses turn right and left, overtake, and reverse generally with warning but sometimes without. Two-wheeled vehicles thread their way precariously between this heavy traffic, and pedestrians cross the roads where they will. In this hostile environment, 149 fatal accidents occurred—87 to pedestrians, 29 to motor-cyclists, 17 to vehicle occupants, and 16 to pedal-cyclists. Of the 34 fatal accidents outside the City of Birmingham, 13 concerned car occupants, 10 pedestrians, 6 pedal-cyclists, and 5 motor-cyclists. This evidence presents a challenge to automobile engineers and body designers to produce vehicles of a safer design for the crowded road conditions that exist in and around our cities, for cars were concerned in the great majority of the accidents of this study.

Pattern of Fatal Road Injuries

The table summarizes 593 significant injuries resulting in the deaths of 183 road users as found at necropsy, an average of more than three per fatality. Since necropsies are performed primarily to establish the cause of death this is a conservative estimate of the numbers of injuries. The Table does not include the very common skin wounds or subcutaneous and muscle-tissue injuries. These are so common as to be almost always present in one or many parts of the body after road accidents. Such injuries can of themselves be fatal. Two deaths to pedestrians resulted from multiple abrasions and contusions to the skin and muscle-tissue alone: one died from haemorrhagic shock not corrected by transfusion, and the other from pulmonary embolism.

Sites of Severe Injuries of Different Categories of 183 Road Users Killed in Accidents

Category of Road Users	Fractures						Major Soft-tissue Injuries									Total Injuries	Complications			No. of Deaths
	Spine	Legs	Arms	Pelvis	Ribs	Skull	Brain	Cord	Kidneys and Adrenals	Lungs	Liver	Spleen	Stomach and Bowel	Bladder and Urethra	Major Blood Vessels		Severe Blood Loss	Pulmonary Embolism	Infection	
Pedestrians ..	15	41	17	31	32	57	67	2	2	27	10	8	5	4	2	320	51	4	16	97
Riders of motor-cycles, scooters, or mopeds ..	4	7	6	8	12	21	22	1	4	11	3	8	6	1	5	119	22	—	2	34
Pedal cyclists ..	1	4	1	—	9	17	19	—	3	6	4	2	2	2	2	72	9	—	—	22
Vehicle occupants	—	1	4	1	10	16	21	1	1	13	4	4	—	1	5	82	13	4	3	30
Totals ..	20	53	28	40	63	111	129	4	10	57	21	22	13	8	14	593	95	8	21	183

Pedestrian Deaths

As in national statistics, the pedestrian in this survey was the most frequent victim. Of the 149 road fatalities in Birmingham, 87 were to pedestrians. Taking the whole series of 183 fatalities in and outside the city, 97 resulted in deaths of pedestrians; cars were the injuring agents in 64 of these, motor-cycles in 13, lorries

*This work is supported by a grant from the Automobile Association.

and vans in 10, public transport vehicles in 9, and an electric milk-float in 1. No pedal-cycle directly caused a pedestrian's death.

In about two-thirds of the collisions between motor vehicles and pedestrians, the front near side of the vehicle, either the head-lamp or front mudguard or near side of the front bumper, first made contact with the pedestrian. In about one-third it was the centre front or centre offside of the vehicle. In some the collision was due to the sudden braking of the vehicle, which then skidded, generally on a wet road surface, and the pedestrian was knocked down by the sides or the rear of the vehicle.

We have found it difficult if not impossible in every car–pedestrian collision to relate the point of first impact of the car with a particular anatomical area of the pedestrian. Yet we are in no doubt that six fatal thoraco-abdominal injuries were caused by the impact of the projecting cowling of the near-side front head-lamp hitting the pedestrian. There were two fatal penetrating brain injuries caused by the rigid pillar of the near-side front mudguard mirror, after the mirror had been knocked off, leaving a sharp rigid piece of metal 2–3 in. (5–7.5 cm.) in length to inflict the fatal injury. So far as we know, there is no reason why head-lamps should have a projecting cowling with a narrow edge often coming to a point, and certainly no reason why a wing mirror should be mounted on a *rigid* metal pillar.

Since the most frequent point of first impact between the car and the pedestrian is the near-side front leading edge of the vehicle it would seem that the driver's field of vision over this area could, with advantage to the pedestrian, be improved. In a great number of lorries the field of vision immediately in front is extremely bad. In this study at least two lorry drivers did not see the child pedestrian cross suddenly in front of their lorry as it moved off from the stationary position at the road-side.

The severity and multiplicity of pedestrian injuries would seem to depend first upon the force and the site of impact, next upon the part of their body that then hits the road, road furniture, or other vehicles, and whether or not they are run over. In short, there is a series of violent impacts before the pedestrian's body comes to rest. If the first impact of the vehicle is low on the pedestrian's body the pedestrian is generally thrown up into the air to land either on the road or on the bonnet of the car. If the first impact is higher the pedestrian is knocked forwards and downwards. At the beginning of this survey we supposed that it would be less damaging to the pedestrian if he was thrown upwards, landed on the bonnet of the vehicle, was carried forward, and then gently fell off as the car came to a halt. But an analysis of the injuries does not confirm this theory. For example, one 48-year-old woman was subjected to this sequence of events and sustained serious fractures of the legs, arms, spine, ribs, and pelvis, severe lacerations of both lungs, the liver, spleen, bowel, bladder, and urethra. Clearly the severity and multiplicity of pedestrian injuries depend upon a sequence of violent impacts.

Some points of criticism of existing car design have been mentioned because they are so easily remedied. However, this study shows quite clearly that the behaviour of many pedestrians (not so easily remedied) was a contributing cause of their accident. Reviewing the 97 pedestrian deaths, we have evidence that 48 were not looking as they were crossing the road, or began to cross from behind vehicles parked at the roadside and came into the view of a driver with the car only a few yards away. Some were running, sometimes in fear of the dangerous position in which they had placed themselves, and many neglected to use pedestrian crossings very close at hand.

The main offenders were those whose age makes such behaviour difficult to understand: 57 were 65 years or over, 29 of these being 75 or more and 15 being 80 or more. In short, 62% of all pedestrian deaths in and around a provincial city were of old people. They did not die because they were old but because they suffered multiple severe injuries. The sex distribution showed no difference between old men and old women.

More readily understandable is the careless road behaviour of young children. There were 12 deaths in children under the age of 10, 5 of these being under the age of 4, and one was a 24-months-old boy who ran into the road to retrieve his ball. The majority of these children were running across the road completely disregarding its risks; many of them were playing. Among the children's deaths, one baby was killed in its pram just after it had cleared the kerb with the mother still on the footpath. One wonders if kerbs are necessary at pedestrian crossings, for a mother's attention must first be concentrated on getting a pram over the kerb before crossing the road.

Bad and unsafe driving behaviour was also a contributing cause in car–pedestrian collisions. Excessive speed, having regard to the crowded road conditions in a city, particularly when approaching pedestrian crossings, and taking undue risks at road junctions, especially when overtaking other vehicles, were among many examples of the lack of a driver's consideration to other road users.

Deaths to Motor-Cyclists

The overall pattern of motor-cyclists' injuries is again one of severity and multiplicity, as shown in the Table, with a high incidence of brain, lung, and major mediastinal injuries. In this group of 34 motor-cyclists' deaths there were two ruptured hearts and two ruptures of the aorta. One other major vascular injury was a complete division of the common iliac artery and vein of a pillion rider through direct impact against the sharp rear off-side end of a stationary lorry.

The age and sex distribution shows a radical change from that of pedestrian road deaths. Of the 34 motor-cycle and pillion-riders killed, 21 were under the age of 25 (18 were in the 16–22 age-group); there were only four over the age of 45, and the eldest was 55; 30 were males and 4 females. Twenty-eight deaths involved the driver and 6 the pillion passenger. Of the total deaths 26 followed ejection from the machine, in 6 cases the driver remained on the machine, and in two a doubt exists. After ejection seven motor-cyclists were run over by other road vehicles. Twenty-four motor-cycle deaths resulted from collisions with cars or lorries, often only a glancing impact as a motor-cyclist tried to overtake through a narrow gap. On two occasions motor-cyclists received fatal injuries after collision with pedal-cyclists. On seven occasions no other vehicle was involved, five of these motor-cyclists making violent contact with road furniture, lamp-posts, walls, or fences, and one struck the kerb. On one occasion a motor-scooter rider got

into a speed wobble on a cobbled road, was ejected over the handlebars of his machine on to his head, receiving fatal brain injuries. He was not wearing a crash helmet.

Of the 34 motor-cyclists and pillion passengers who died, 19 were not wearing crash helmets and 14 of these sustained severe brain injuries. Of the 15 wearing crash helmets, 8 sustained some degree of brain injury. The wearing of an efficient helmet will not prevent fatal brain injury when the forces involved are very great. For example, one motor-cyclist wearing a crash helmet and travelling at considerable speed collided head on with a lorry travelling in the opposite direction and died from a head injury. Our evidence, however, suggests that even among fatal cases fewer severe head injuries occur to motor-cyclists wearing crash helmets.

The two ruptures of the heart—one in a rider and the other in a pillion passenger (not on the same machine)—resulted from hitting roadside furniture at considerable speed—in one a stone gate-pillar and the other a lamp-post. Neither was killed instantaneously—one survived eight hours and the other over 48 hours.

The overall picture of death on powered two-wheel vehicles is of youth taking risks at speed, sometimes at very considerable speed, both inside and outside the city.

Deaths to Occupants of Motor Vehicles

There were 33 deaths to the occupants of motor vehicles, but, as noted above, three of these occurred from natural causes and were not associated with any significant injuries. Taking the road deaths as a whole and considering the number of motor vehicles on the roads, this evidence indicates that the least dangerous place to be on the road is within a motor vehicle, and the bigger the vehicle the safer it is. All the vehicles involved were private cars, with the exception of one taxi, one van, and one person who was killed in a public transport bus. Our evidence does not include the number of occupants in all the vehicles involved in fatal accidents, but we understand that the average car occupancy in this country is approximately two per private vehicle. (In America it is known that the average occupancy per private vehicle is 1.2.) Clearly the driver must always be at risk, front-seat passengers frequently, and back-seat passengers infrequently. In this series the driver was the victim in 13, the front-seat passenger in 10, and the back-seat passenger in 7. Of the 13 drivers, 12 were males; 6 were under the age of 30, 4 were from 30 to 49, and 3 from 50 to 60. Twelve car occupants received their fatal injuries after being ejected out of the vehicle; the others remained in the vehicle. Some of the latter cases presented considerable difficulties to the police and ambulance crews in removing occupants from trapped positions within their cars. On several occasions the car, together with its occupants, was trapped and wedged under the tail of a heavy stationary lorry.

Again in this survey of injuries to car occupants we have found it impossible always to relate the nature of the injury with a specific feature of car design. For example, a car skids on a greasy road, hits the rear end of a heavy lorry, overturns, skids on its side to the other side of the road, and is there hit by an oncoming car. The rear-seat passenger in the skidding overturned car dies of multiple injuries. From the nature of this accident it is clear that this occupant was thrown all around the car, hitting many of its interior features. It is known that his head finally went through the roof but that he fell back inside the vehicle. We further know that he suffered severe injuries to the scalp, skull, and face, ruptures of the liver and spleen, severe lacerations of the left lung, and multiple fractures of the ribs and arms, but we cannot relate these injuries precisely to the various internal features of the car.

Our series includes several equally confusing pictures of fatal injuries to car occupants. Often, however, there is quite clear-cut evidence that has allowed us to relate the injuries to the injuring object. There were six injuries undoubtedly due to impact of the driver against the steering-column. We have photographic evidence of the displacement of the steering-column and the deformation of the steering-wheel, and can associate these exactly with fatal lung, mediastinal, or other injuries. Lung and mediastinal injuries were not invariably associated with fractured ribs. Inside the ribs the soft-tissue injuries were always multiple. Of the six steering-column deaths, two included ruptures of the heart and one included ruptures of the aorta and the inferior vena cava. All had severe lung injuries. In another the car travelling at considerable speed was brought to a sudden halt by hitting a lamp-standard, after which the driver was ejected from his seat upwards and forwards; at the same time the steering-column was displaced upwards and backwards; it missed his chest but impaled his head against the roof. Among other facial and head injuries, this driver's tongue was found loose in the middle of his pulped brain. On the evidence of these six fatal steering-column injuries one wonders why more attention is not paid to the safer design of steering-columns by *all* car manufacturers.

There were 12 fatal car-to-car collisions at road junctions, when the front of one car hit the side of another. If the passenger compartment of a car hit on its side is of light material and the point of impact directly against its occupants, the possible consequences of severe injuries due to direct violence are obvious. For example, a 24-year-old female driver of a very light car was involved in a collision at a road junction, and the bodywork of her car was badly dented directly opposite her right side. She suffered from multiple fractures of the right ribs, a deep laceration of the right lung, her liver was torn almost in two, her right adrenal gland was badly bruised, and the spleen suffered superficial tears. This slightly built young woman with a normal blood volume of approximately 4 litres had lost, by measurement at necropsy, 2.5 litres of blood into the peritoneal cavity and 1 litre into the right pleural cavity. If one assumes that loss of blood occurs only when the victim is living, this is a remarkable amount to lose before death. She was dead when taken from her car.

It will be noted in this series of city accidents there were almost as many fatal injuries due to side collisions as to head-on collisions. As might be expected from direction of impact, more than half of these people were ejected from their vehicle. None was wearing safety-belts.

The current trend of car design is towards increasing power/weight ratio. Weight is reduced where possible. Yet in the interests of the safety of the occupants there should be a minimum standard for the strength of the passenger compartment. So long as the passenger compartment remains intact, and the occupants remain inside the vehicle, they can be more safely "packaged."

If the passenger compartment collapses they are exposed to the full violence of impact or may be killed as a result of their ejection from the vehicle.

In eight of the accidents causing death to car occupants no other vehicle was involved. In four of these alcohol was the major factor, and in at least one other it probably contributed to the accident. All these cars went off the road to overturn or hit roadside furniture.

Deaths to Pedal Cyclists

When one observes pedal cyclists wending their dangerous way between the heavier vehicles on crowded city roads one wonders why they run such risks. So much depends on their balance, the power of their legs, a cool head, and undoubted courage. Considering the number of pedal cyclists on city roads their death-rate is very high. In this series there were 22 deaths to the riders of pedal cycles; 16 occurred in Birmingham and 6 in neighbouring districts. Nine of the victims were boys under the age of 16 and the eldest was 59. The risks of riding a pedal cycle at any age among the busy traffic of a city is best illustrated by a lifelong cyclist of 51, who met his fatal accident on returning home for lunch. His bicycle went over some loose stones left near the gutter; as a result he became unseated, fell to his off-side, and was run over by the rear twin wheels of a passing heavy lorry.

Of the 22 pedal cyclists all but one were males; 12 were killed instantly or were dead on arrival at hospital. The general pattern of their injuries was no different from that of other road fatalities; they were severe and multiple. Eighteen received their injuries after being thrown from their bicycle, after which 7 were run over—4 by lorries and 3 by cars. It is of interest to note, as shown in the Table, that head injuries are as common in pedal cyclists as they are among motor-cyclists. No pedal cyclist in this series was wearing a crash helmet; indeed, we have never seen a pedal cyclist wearing a crash helmet.

Four of these pedal cyclists were boys aged 5, 7, 12, and 15. From the evidence it appears that three of these lads became unbalanced through losing their nerve as a heavy lorry passed very near; certainly there was no evidence of a collision. Each fell off his bike, to be run over by the twin rear wheels of a heavy lorry and killed instantly; the fourth boy was run over by the rear wheels of a car and killed instantly.

On this evidence one wonders why the law should permit young children to ride pedal cycles on our crowded city roads, and permit the body structure of some lorries such a high clearance from the ground.

Discussion

This study of the nature and causes of 183 fatal injuries to road users in and around Birmingham in 1960 is not sufficient by itself. We have yet to analyse our collected data of the nature and the causes of much greater numbers of trivial and severe injuries for the same year. Similar and related studies will continue for at least the next six years. Yet the study does confirm two main impressions based on our hospital's 20 years' experience in treating over 80,000 road accidents.

The first is that most road accidents are due to errors of behaviour by all types of road user. This emphasizes the need to continue educational campaigns now being waged by various organizations and individuals in this field.

The second is that attention must be paid sooner or later to improving the standard of safe design of all road vehicles. A Bill to this end was presented to the last Congress of the U.S.A.; it passed the House of Representatives but not the Senate. A modification of the Bill is to be reintroduced to the current session of Congress. The automobile industries of America opposed this Bill on the grounds that they should be left to set their own safety standards. Mr. Karl M. Richards (1961), of the Automanufacturers Association Inc., writes: "To make design mandatory will restrict development rather than promote it; it will make the engineer's goal one of designing to conform to inflexible, sometimes outdated codes rather than solving basic problems . . . it will discourage rather than stimulate research and development in automotive safety."

While giving due consideration to this argument, it would seem unrealistic to expect self-regulation in the highly competitive field of selling motor vehicles. What would happen, for example, if a public-spirited car manufacturer decided to make less powerful, more manageable, yet not unattractive cars—a manufacturer who incorporated safety features that increased the cost of his product while all his rivals were free to disregard even the fundamentals of safe design and offer the public a much cheaper vehicle with all the eye-catching "selling gimmicks"? The public-spirited manufacturer and his agents would almost certainly lose money. Surely some principles of safer car design must be followed by *all* manufacturers. From the evidence of this survey alone it would seem that car–pedestrian collisions would be fewer and less severe if:

(*a*) The car driver had a better forward field of vision, particularly over the front near side of the vehicle. This was the area of first impact in the majority of fatal car–pedestrian accidents here analysed. The front of the bonnet and mudguards should slope downwards so that even small children immediately in front of the car could be clearly seen.

(*b*) The average car driver would be helped in avoiding these impacts with pedestrians if the steering and general control of the vehicle was improved, as seems possible in the Ferguson prototype four-wheel-drive car.

(*c*) Improvement in control during braking by eliminating the risks of skidding would seem possible with the Maxaret braking device, which can be conveniently combined with a four-wheel drive. A lessening of the violence of the first impact with the pedestrian would be a major factor in decreasing the severity of injuries.

(*d*) This study produces evidence of the dangers to pedestrians of sharp external fittings on the vehicle. These should be eliminated, with particular attention to the sharp head-lamp cowling, rigid pillar mudguard mirrors, and sharp projections on the bonnet.

(*e*) On the evidence of this study, lorry design could be improved by giving the driver a clearer forward vision immediately in front of his vehicle and by bringing the body closer to the ground in order to avoid the rear wheels running over people ejected from other road vehicles.

This study of deaths of car occupants indicates that designers should note:

1. That ejection out of the car resulted in 12 of the 30 deaths analysed. This is clear evidence in favour of the value of safety-belts. If these are to be acceptable to all car users—that is, easy to put on, wear, and take off—they should preferably be incorporated as an integral part of seat design. This would mean, among other things, improvements in attachment of seats to the body.

2. The strength of the bodywork of the passenger compartment should not be below a certain standard. Side-on collisions at road junctions are common. This study shows that a fragile car body has caused the deaths of car occupants.

3. More attention should be paid to the safer design of the traditional form of steering column. We have recorded the deaths of six drivers from this cause—that is, 6 of the 14 deaths of those who remained in the car after the collision.

4. The secure fixation of all seats and all cushions. We have evidence that on more than one occasion *all* the seats came free and moved forward to jam the front-seat occupants under and against the dashboard, with fatal results.

5. After all types of collision and roll-over accidents car occupants are thrown about within their enclosed metal box, hitting any of the projecting internal fittings—hence the multiplicity of their injuries. There should be no projecting internal fitting. Efficient padding should be provided at the most important sites of impact—this is, the junction of the roof and windscreen, including the back of the sun visor, the dashboard, and the back of the front seats. The padded surfaces should be as flat as possible. Padding which merely hides projecting edges, common in many cars, is undesirable.

6. Several of the fatal accidents studied resulted from collisions at night between cars and the rear of stationary lorries. The length of overhang is sometimes so great that occupants are injured directly by the rear of the lorry. Limitation of this overhang should be practicable. A light under the rear of lorries might help by giving a clear silhouette of width and shape. There is need, too, for a standardization of rear lights, their position, colour, and intensity.

7. Since many of the fatalities studied were due to excessive speed in and outside the city, there is a case for an auditory warning when speed exceeds 30 m.p.h. in built-up areas, and perhaps 60 m.p.h. on the open road.

Medical research and repair surgery have yet to meet the full challenge of ever-increasing numbers of road accidents, numbers that may double the present figure by the end of the next decade.

Early in this research we realized the great value of necropsy reports to any study relating road injuries to their cause. Yet necropsies undertaken for the purpose of forensic medicine are not intended to uncover the presence of *all* injuries, much less their detailed anatomy.

A detailed study of necropsy material would be invaluable for research into injuries of all types, providing data on which further advances in methods of treatment as well as improvements in prevention could be soundly based.

A department within the proposed accident research and teaching centre (Gissane, 1955, 1961) could therefore well combine the facilities required for the coroner's necropsies and those for careful radiological studies of the skeletal and vascular systems and for dissection and microscopical examination of the precise nature of all injuries. Judging from the numbers of necropsies for road deaths carried out in Birmingham in 1960, such a department would be fully occupied. From preliminary discussion with interested authorities, nothing but co-operation is anticipated in this attempt to help in the solution of the major medico-social problem of this century.

Summary

The coroner's files of all deaths in the City of Birmingham due to road accidents in 1960 have been studied. Of the 183 cases, 53% were pedestrians, 19% motor-cyclists, 12% pedal-cyclists, and 16% vehicle occupants. Where possible, findings have been correlated with clinical records and with details of the accidents obtained on site.

Multiple severe injuries were a feature of the necropsy findings in all types of road user. Head and thoraco-abdominal injuries predominated. On average there were more than three severe injuries per fatality.

Pedestrians were most often struck by the front-near side of vehicles, and in several cases fatal injuries were caused by projections on this part of the vehicle. Fatal pedestrian accidents were commonest in the aged.

The majority of motor-cyclists who died were under 25 years of age. Most of them were thrown off their machines, receiving fatal injuries, often to the head or thorax, due to the impact or to subsequently being run over.

Many of the deaths of occupants of motor vehicles were due to their being ejected. Among the others, impact with the steering column, roof, and dashboard commonly caused fatal injuries. Side-on impacts caused severe injuries, particularly in vehicles with light bodywork.

Deaths of pedal-cyclists were often due to their falling off their machines. Several of them were then run over in the heavy city traffic.

In the light of these findings, improvements are suggested for the design of both the exterior and interior of vehicles to prevent or reduce such injuries.

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On August 4 last year, the Minister of Agriculture, Fisheries and Food and the Minister of Health made the Authorized Officers (Meat Inspection) Regulations, 1960, which had the effect of creating a new type of officer who could be employed by local authorities in England and Wales as meat inspectors with full powers to examine and seize meat. The qualification required was a special Certificate in Meat Inspection issued by the Royal Society of Health. The Ministers have now decided to add two further qualifications: the Certificate in Meat Inspection issued by the Royal Sanitary Association of Scotland, and the Certificate for Meat Detention Officers in Northern Ireland issued by the Royal College of Veterinary Surgeons. They have accordingly made the Authorized Officers (Meat Inspection) Regulations, 1961, which came into operation on March 10, and which re-enact, with the necessary amendments, the 1960 regulations. The recognition of these two further qualifications will mean that a useful, though perhaps numerically small, source of manpower will become available to local authorities for meat inspection duties. Copies of the regulations (S.I. 1961, No. 368) are obtainable from H.M.S.O., price 3d. (by post 5d.).

NEONATAL TETANUS IN SIERRA LEONE

BY

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This report is the result of an analysis of 114 consecutive cases of neonatal tetanus treated at the Nixon Memorial Hospital over the period of five years seven months preceding September, 1960. Approximately half-way during this time chlorpromazine therapy was introduced, and one purpose of this paper is its evaluation in this condition.

The town of Segbwema is in the South-Eastern Province, 260 miles (420 km.) from Freetown, and has a population of about 4,000. Its 130-bed Mission Hospital serves a wide area. In 1959 there were 86,000 out-patient attendances and 3,000 patients were admitted.

Ecological Background

The people comprise a predominantly agricultural community, apart from chrome mines 30 miles (48 km.) away and diamond mines 60 miles (96 km.) away. Most of the patients come from villages of fewer than 500 people. There are no horses and few cows in this area, but it is common to see goats, hens, sheep, and sometimes pigs wandering around the houses. At night the hens are taken indoors, and other animals often shelter on the veranda. The usual method of disposal of human faeces is by a pit latrine; this is frequently too shallow and often attracts flies.

There are relatively few trained village midwives, and, so far as is known, all the cases here discussed were delivered by traditional village midwives—usually Bundu Society elders. Birth usually takes place on a grass mat spread on the earth floor of a mud-walled thatched house. According to the custom of the local Mende tribe, as soon as the baby is born a woman will run to the village and borrow a particular knife kept by an old man; the knife may be hanging in a raffia bag on the wall, on the top of a cupboard, or in a box together with other possessions. The umbilical cord is tied with native spun thread, then "medicine" is applied by the midwife, and subsequently each morning by the grandmother. The application usually consists of the juice from a young banana shoot, squeezed out by rolling it between the hands. Sometimes leaf fragments are added. It is interesting to note that the banana trees are commonly grown behind the native houses; it is customary to throw house sweepings and refuse around the bottom of the trees, and animals root among this in search of food scraps. A young banana shoot originates from its parent stem below ground and thus comes into close contact with the debris around the tree base.

Description of the Present Series

The only selection in this series has been to exclude six cases which were so mild that a diagnosis of tetanus was disputable; all but one of these recovered. During the same period of time 11 cases of tetanus were diagnosed in older children or adults, and these too are not discussed.

Most of the 114 cases were severe: of the patients who died the average duration of life after admission was 2.4 days. There were 60 boys and 54 girls. Of the cases studied in the five completed years, 51 occurred in the wet season (May–October) and 32 in the dry season (November–April)—a finding different from that of Trowell and Jelliffe (1958) and Tompkins (1958), who reported a predominance of cases in the dry season.

The average age on admission of those who lived was 10.5 days, whereas for those who died it was 6.3 days; these figures should be regarded as approximate only, for the local people do not "number their days" with our sense of accuracy. Almost all the mothers stated that the trouble had started on the previous day, and it has not proved possible to analyse the number of hours between onset of symptoms and commencement of treatment. Trismus, causing inability to suck, was usually stated to have been the first sign, and this was quickly followed by widespread muscular rigidity, severe spasms being provoked by attempted passive movement of flexed limbs. In advanced cases very minor stimulation provoked spasms.

Nursing Care

The importance of expert and gentle nursing cannot be overemphasized, for it is vital to recovery.

General Care.—The child is nursed on its side, lying horizontal, but is turned every two or three hours. So far as possible all nursing treatment is synchronized so that the baby is minimally disturbed. Handling is gentle and ideally the room should be quiet.

Feeding.—Expressed breast milk is given through a fine-bore nasogastric tube. Oral spoon-feeding is impossible in a severe case, and inadvisable in moderate cases because of the necessity for very frequent feeds, with the inevitable accompanying stimulation and the danger of inhalation pneumonia.

Care of Umbilicus.—The umbilicus is thoroughly cleansed with hydrogen peroxide on admission, then a dry dressing is applied. Sometimes marked stump infection makes daily cleansing necessary. Local surgery or antitoxin injection have not been employed.

Oral Hygiene.—Trismus renders routine measures impossible, but mucus accumulating in the pharynx is removed with an extractor.

Drug Therapy

Chlorpromazine.—This was given by four-hourly 10-mg. intramuscular injections until spasms were controlled—usually for 24 hours, but sometimes longer—then a 10-mg. injection was given six-hourly until there was obvious improvement in the tonic rigidity and general condition, when an eight-hourly dosage was substituted. If reduction in frequency of dosage was followed by reappearance of spasms a shorter interval was readopted. The last 70 children were treated in this way. The average duration of such therapy for those who recovered was 9.6 days, and on one occasion was prolonged for 17 days.

Antitetanus Serum.—This has been given to all patients, usually in a single dose of 10,000 units on admission; but prior to the use of chlorpromazine dosage varied between 20,000 and 50,000 units, depending on severity.

Penicillin.—All cases were given oily penicillin, usually 300,000 units at once and 150,000 units daily for five days. If there was marked umbilical sepsis or if chest complications supervened, a larger dosage was used, and crystalline penicillin given in addition.

Sedatives.—(*a*) Prior to the introduction of chlorpromazine either chloral, potassium bromide, or a combination of these was used routinely, 2 gr. (0.13 g.) of each up to four-hourly if necessary. Injections of phenobarbitone sodium, ½–1 gr. (16–32 mg.), were given to 7 out of 44 patients, and paraldehyde injection, 15 min. (0.9 ml.), was given to one child only. (*b*) After the introduction of chlorpromazine no other sedatives were given from June, 1958, until the beginning of 1960, apart from phenobarbitone on one occasion. But in 1960 all children were given chloral, 2 gr. (0.13 g.) p.r.n., an occasional dose being allowed between injections of chlorpromazine if spasms recurred. In this year also two children were given injections of phenobarbitone sodium, ½–1 gr. (16–32 mg.), and one child was given an injection of paraldehyde.

Mephenesin ("myanesin").—Before the use of chlorpromazine 24 children were given elixir of mephenesin orally or through nasogastric tube. The usual dose was 1 dr. (3.5 ml.) six-hourly. After chlorpromazine was brought to use, mephenesin therapy was discontinued.

Results

Before Use of Chlorpromazine.—Of the 44 patients treated without chlorpromazine, 12 (27.3%) lived and 24 (54.5%) died in hospital. Eight were taken away against advice, and almost certainly died, making the probable mortality 72.7% (Table I). Of 24 children

TABLE I.—*Annual Analysis of Cases*

	1955	1956	1957	1958		1959	1960
				Chlorpromazine			
				Without	With		
Lived	3	4	3	2	13	10	13
Died	7	4	4	9	2	7	13
Taken away:							
Worsening ..		2			1	1	3
Improving ..						3	1
Condition not recorded ..	3			3	1	1	1
Total ..	13	10	7	14	17	22	31

to whom mephenesin was given, 5 (20.8%) lived, and 19 (79.2%) died. The average stay in hospital of those who lived was 13.2 days, of those who died 1.9 days, and of those taken away against advice 3 days.

After Introduction of Chlorpromazine.—Of the 70 patients treated with chlorpromazine, 36 (51.4%) lived and 22 (31.4%) died in hospital. Twelve were taken away against advice, and most likely died, although 4 were showing signs of improvement. The probable mortality was therefore 48.6%. The average stay in hospital of those who lived was 14.7 days, of those who died 3 days, and of those taken away against advice 3.6 days. One child developed jaundice after two days of treatment and was taken away against advice on the third day.

The proportion of babies taken away against advice was similar for both periods—18.2% in the first period and 17.1% in the second. The increase in the percentage of babies living was statistically significant, the difference being 24.1 ± 9.5.

Subsequent History

Detailed follow-up of all the patients who recovered has not been possible; but the subsequent records of 34 successful chlorpromazine-treated cases have been examined.

Ten children living locally were advised to attend the weekly baby welfare clinic held at the hospital; all were alive and well at the time of writing. Four have been seen for more than 12 months after discharge, three for between 6 and 12 months, and three between 1 and 3 months.

Most of the other children came from homes situated many miles away, often in inaccessible little villages, and they would normally not be seen again at hospital unless they contracted a further illness. Of the 24 cases in this category we have records of seeing only nine subsequently—five after more than 12 months and two after between 3 and 12 months—none of these has had trouble referable to tetanus or its treatment. Of two other patients the records note residual stiffness in one after four days, and failure to gain weight in the other at 10 days after discharge, and in each case there was no subsequent attendance.

Therefore of the 34 cases we have satisfactory subsequent records of three months or longer in 16. The majority of the others may well be alive, but their inaccessibility makes it impracticable to verify this. It may be noted here that in this area the overall child mortality from all causes under the age of 5 years is 62%.

Discussion

Exact statistical analysis is often difficult in the local circumstances of tropical hospitals. It is much more regrettable from a humanitarian viewpoint that of the 114 children 20 were taken away from hospital against medical advice after a very short therapeutic "trial period." If death is likely to take place, the Mende people prefer this to be in the home rather than in the hospital. It is encouraging to note an annual decline in this custom, reflecting as it does more than just a growing confidence in technique. Again, it may be noted with astonishment by some that the average stay in hospital was only about a fortnight. This also must be viewed in context: the economic domestic need of the mother to return home as soon as possible; also there is a constant need to admit so many seriously ill children.

Methods of nursing treatment have been comparable throughout this series of cases. There seems to be no reasonable doubt that chlorpromazine therapy has been responsible for a reduction of mortality from 72.7% to 48.6%. In this statement the death of those taken away against advice is assumed. Had they remained in hospital some undoubtedly would have lived. Thus in more ideal conditions this mortality figure should be much lower. Yet a review of the literature shows that it is usually much higher in this disease. Even with the use of chlorpromazine it is often between 70 and 95% (Table II). A comparison of the mortality figures can be misleading, since there may be more than one variable element between two series of cases. Apart from possible alterations in the virulence of infection in different localities, it is felt that three factors merit discussion.

1. *Incubation Period.*—If we equate the incubation period and admission age, then 10.5 days is longer than many reported. We would agree with the statement of Spivey *et al.* (1953) that the prognosis is relatively much better with an onset of tetanus after rather than before the seventh day of life. But an assumption that the infection was necessarily introduced at the time of cord severance is not necessarily correct, because a potentially highly infected application was used on the cord daily thereafter.

TABLE II.—*Reported Mortality of Treated Neonatal Tetanus*

	Author	No. of Cases	Mortality
Without chlorpromazine	Vinnard (1945)	11	55%
	Jelliffe (1950)	25	96%
	Spivey *et al.* (1953)	26	77%
	Lorenz (1957)	19	58%
	Pinheiro (1957)	256	77·3–92·5%
	Tompkins (1958)	141	89·6%
	Adams *et al.* (1959)	20	90%
With chlorpromazine	Laurence *et al.* (1958)	31	93%
	Adams *et al.* (1959)	20	95%
	Wright (1960)	34	94%
With chlorpromazine and barbiturate	Sarrouy *et al.* (1956)	20	80%
	Earle and Mellon (1958)	32	25%
	Adams *et al.* (1959)	44	71%
	Wright (1960)	77	76%

2. *Dosage of Chlorpromazine.*—Adams *et al.* (1959) note that there is a "maximal dose above which antitetanus activity is not increased, and indeed the tetanus may be increased at very high doses." They used 25 mg. intramuscularly up to four-hourly, and the mortality was 95%: commenting on this, they observed that "overdosage cannot be excluded as a cause of death," and subsequently in a selected group of 44 cases used 100 mg. in divided doses daily, supplemented by sodium phenobarbitone, with a mortality of 77%. Wright (1960) used 100–200 mg. daily, with a 94% mortality; but with a reduced amount of 12.5–100 mg. daily and the addition of sodium phenobarbitone the mortality fell to 76%. These reports were from South Africa. Earle and Mellon (1958) reported a 25% mortality in 32 cases in Haiti. All fluid requirement for the first six to eight days was given intravenously, and to this was added chlorpromazine, 1 mg./kg. four-hourly, supplemented by sodium phenobarbitone. Sarrouy *et al.* (1956), in Algeria, used a chlorpromazine dosage of 2–3 mg./kg. together with phenobarbitone, with a mortality of 80%. After a great deal of experimental and clinical experience in the therapy of this disease, Laurence (1958) deduced that beyond 3–5 mg./kg. the condition was likely to be worsened. The particular dosage described in the present series was largely empirical initially, and we have sometimes had to resist the temptation to increase the amount. It is approximately 4.5 mg./kg. (10 mg./lb.) daily to start with, declining to 2.3 mg./kg. (5 mg./lb.) daily later, in divided doses, intramuscularly. This was sufficient to control spasms fairly well in most cases, but in 1960 the occasional addition of chloral by nasogastric tube helped some children to rest better between injections, and the slight rise in mortality as compared with 1959 is not significant. In this connexion it may be noted that in the latter part of 1958, when the new chlorpromazine therapy had been introduced at the hospital, the mortality in 17 cases was under 25%.

3. *Barbiturates.*—Over the past 20 years in this hospital the accumulated clinical impression of a number of workers has on the whole been unfavourable towards the routine use of barbiturates in neonatal tetanus. At one time paraldehyde was in common use in preference to phenobarbitone. In the 70 chlorpromazine-treated cases of this series one or two small doses were given to each of three patients only. It is not the purpose of this paper to evaluate barbiturate usage in neonatal tetanus, but the evidence presented does not support the statement by Wright and Adams (1960) that chlorpromazine is "useful in the treatment of this most severe form of the disease only when combined with a barbiturate."

There are two more therapeutic points of interest in this series: (1) Pinheiro (1957) described a lowering of mortality from 92.5% to 77.3% with the use of mephenesin intravenously. In the present series mephenesin elixir was given orally or by nasogastric tube without improvement in prognosis. (2) The high dosages of antitetanus serum in earlier years have now fairly generally been abandoned. In the present series a single dose of 10,000 units was found adequate.

In the face of the extremely high mortality figures reported for this disease, curarization and the use of an intermittent positive-pressure respirator is on trial in a number of centres (Glossop and Low, 1957; Lawrence and Sando, 1959; Smythe and Bull, 1959; Poulsen and Nørby, 1959; Alhady *et al.*, 1960). But the majority of cases of tetanus neonatorum occur in areas of the world where hospitals do not have these facilities. The present series suggests that with a particular dosage of chlorpromazine the position might not be quite as bad as formerly thought. Even so, a mortality figure between 31% and 48% is very serious. Our reaction to the present situation is to train more local village midwives, even of a poor educational background if necessary, and to carry out a programme of simple instruction in hygiene for the village people.

Summary

A series of 114 consecutive cases of neonatal tetanus treated at the Nixon Memorial Hospital, Segbwema, Sierra Leone, is reported. Seventy infants were treated with chlorpromazine and 44 without: in the latter group 24 were given mephenesin. The ecological background is described.

The introduction of chlorpromazine therapy enabled the mortality to be reduced from 72.7% to 48.6%. These figures would probably have been lower, but 20 children were taken away against advice, and are assumed to have died. Nevertheless the mortality is less than some other series recently reported: in trying to assess the reason for this in the chlorpromazine group, it is thought that the optimum dosage is a factor of considerable significance in neonates.

My thanks are due to all members of the hospital staff who assisted in making clinical information available, and to Dr. W. J. Martin, of the Statistical Research Unit of the London School of Hygiene and Tropical Medicine.

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DEFECTIVE BIOSYNTHESIS OF OVARIAN STEROIDS IN THE STEIN–LEVENTHAL SYNDROME

BY

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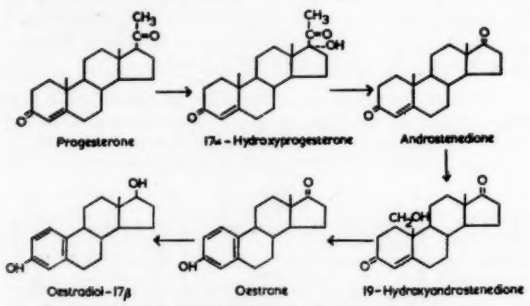
Although the Stein–Leventhal syndrome was first described in 1935 (Stein and Leventhal, 1935), its aetiology is still obscure and its treatment empirical. There can be little doubt that the associated hirsutism is due to an increased production of androgens, and there has been much discussion on whether they are of adrenal or ovarian origin. The studies of Gallagher *et al.* (1958), Prunty *et al.* (1958), Perloff and Channick (1959), and Shearman *et al.* (1961) have all suggested that the adrenals may be involved. On the other hand, there is much circumstantial evidence to implicate the ovaries; for example, the condition responds successfully to such varied surgical procedures as ovarian wedge resection (Stein, 1955), ovarian eversion (Ingersoll and McDermott, 1950), or ovarian medullary resection (Allen and Woolf, 1959).

With the recent elucidation of the pathways of oestrogen biosynthesis in the ovary (Meyer, 1955; Solomon *et al.*, 1956), it became apparent that at least



Biogenesis of oestrogens in the ovary.

one androgen, androstenedione, is normally produced by the ovary as an intermediate in the synthesis of oestradiol-17β from progesterone (see Formulae).

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A method has recently been described for the simultaneous determination of progesterone, 17α-hydroxyprogesterone, androstenedione, oestrone, and oestradiol-17β in small samples of follicular fluid (Short, 1961). Since each of these five steroids has been identified in human ovarian tissue (Zander, 1958; Zander *et al.*, 1959; Smith, 1960), it seemed important to establish the levels of these compounds in the cyst fluid of patients with the Stein–Leventhal syndrome, and to compare them with the levels found in a control group of subjects.

Material and Methods

Cyst fluid was obtained at operation from the ovaries of five patients exhibiting the characteristic features of the Stein–Leventhal syndrome; seven additional samples were obtained from women in whom ovarian cysts or follicles were an incidental finding at laparotomy. After collection the fluid was stored in the deep-freeze until it could be assayed.

Four of the five Stein–Leventhal patients were shown by pelvic radiography after pneumoperitoneum to have enlarged ovaries before submitted to laparotomy. In addition, a number of routine urinary hormone assays were carried out on these patients as further aids to the diagnosis of the syndrome. 17-Ketosteroids were determined by the method of Gibson and Norymberski (1954), and 17-ketogenic steroids by minor modifications of the method of Norymberski *et al.* (1953). Pregnanetriol (5β-pregnane-3α:17α:20α-triol) was determined by the method of Bongiovanni (1954). "Total gonadotrophins" were measured by the method of Loraine and Brown (1956a, 1956b). The atlas of Greulich and Pyle (1950) was used for the determination of bone age. Progesterone, 17α-hydroxyprogesterone, androstenedione, oestrone, and oestradiol-17β were measured by the method of Short (1961).

Case Reports

Case 1.—Aged 24, menarche at 13; her periods were infrequent, and eventually she became completely amenorrhoeic, with a history of three years' infertility. On examination she was minimally hirsute, with a male distribution of pubic hair. The biochemical findings in the urine were: 17-ketosteroids, 8.8 mg./24 hr.; 17-ketogenic steroids, 13.2 mg./24 hr.; gonadotrophins, 21.5 and 16 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries with thickened capsules, the right ovary measuring 6 by 3.5 by 2.5 cm., and the left 6.5 by 3 by 2.5 cm. A bilateral wedge resection was carried out. Histologically the ovaries revealed a thickened theca interna layer; there was no corpus luteum present. Post-operatively she had regular monthly periods and the temperature chart showed evidence of ovulation; she has recently become pregnant.

Case 2.—Aged 20, menarche at 14; her periods lasted five days every two months initially, but eventually they occurred only once a year. There was a history of four years' infertility. On examination she showed minimal facial hirsuties, with a male distribution of pubic hair; the clitoris was normal. The biochemical findings in the urine were: 17-ketosteroids, 14.7 mg./24 hr.; 17-ketogenic steroids, 5.6 mg./24 hr.; gonadotrophins, 9.5 and 8.5 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries, the right ovary measuring 6 by 6 by 3 cm., and the left 5 by 5 by 3 cm. A bilateral wedge resection was carried out; histologically the ovaries showed a thickened capsule and follicular cysts with a prominent theca interna. Post-operatively she had regular monthly periods.

Case 3.—Aged 16, menarche at 10; her periods lasted five days every six months, and she had been hirsute for four years. On examination she was obese, grossly hirsute, and

had an enlarged clitoris; her bone age was 20 years. The biochemical findings in the urine were: 17-ketosteroids, 13.5 mg./24 hr.; 17-ketogenic steroids, 10.3 mg./24 hr.; pregnanetriol not detectable; gonadotrophins, 28 and 21.5 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries with thick white capsules, the right ovary measuring 5 by 2.5 by 3 cm. and the left ovary 6 by 3 by 2.5 cm. A bilateral wedge resection was carried out; histologically the ovaries showed multiple follicular cysts with thecal proliferation. A post-operative follow-up has not yet been made.

Case 4.—Aged 18, menarche at 12; her periods had always been irregular, lasting for four days every 6–16 weeks. On examination she showed gross hirsuties of the face and legs, with a male distribution of pubic hair; the clitoris was normal, and there was no obesity. The biochemical findings in the urine were: 17-ketosteroids, 14.8 mg./24 hr.; 17-ketogenic steroids, 16.3 mg./24 hr.; pregnanetriol, 2.5 mg./24 hr. The gonadotrophin excretion was not determined. Laparotomy revealed bilateral polycystic ovaries, the right ovary measuring 5.5 by 2.5 by 3 cm. and the left ovary 6 by 2 by 3 cm. A bilateral wedge resection was carried out; histologically the ovaries showed thecal proliferation. There has not yet been a post-operative follow-up of this patient.

Case 5.—Aged 18, menarche at 14; her periods lasted for three days every six months, and the menstrual flow was scanty. She had been hirsute for three years. On examination she showed gross hirsuties of the face, legs, and sacral region, with a male distribution of pubic hair; her bone age was normal, and the clitoris was not enlarged. The biochemical findings in the urine were: 17-ketosteroids, 14 mg./24 hr.; 17-ketogenic steroids, 4.3 mg./24 hr.; pregnanetriol, 0.8 mg./24 hr.; gonadotrophins, 4.5 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries about twice the normal size. A bilateral wedge resection was carried out; histologically the ovaries showed follicular cysts and some thecal hyperplasia. A post-operative follow-up has not yet been made.

Comment

All these patients conform to the clinical pattern of the Stein–Leventhal syndrome (Stein, 1959). They all had oligomenorrhoea or amenorrhoea, were hirsute, and had enlarged polycystic ovaries with thickened capsules. The histological sections all showed follicular cysts and thecal hyperplasia. The two women who were operated on long enough ago for there to have been an adequate follow-up both developed regular monthly periods, and one of them has since become pregnant.

There was no suggestion that any of these patients might have been suffering from the adrenogenital syndrome or a virilizing adrenal carcinoma. Although the urinary pregnanetriol of Case 4 was slightly elevated, subsequent investigation (Brooks and Prunty, 1961) showed that the 17-ketogenic-steroid/pregnanetriol ratio was not similar to that found in cases of adrenal virilism. Even though the gonadotrophin levels are usually normal in the Stein–Leventhal syndrome, they are occasionally elevated (Prunty *et al.*, 1958; Stein, 1959; Ingersoll and McArthur, 1959), as they were in Cases 1 and 3.

Controls

The case histories of the seven patients who served as controls are given below. Care was taken to select women who did not show any of the physical manifestations of the Stein–Leventhal syndrome.

Case 6.—Aged 34. A total hysterectomy was performed for menorrhagia 12 days after the commencement of her last menstrual period; histologically the uterus showed a normal proliferative endometrium. Fluid was obtained from numerous small follicles in both ovaries.

Case 7.—Aged 36. She had a history of irregular cycles with occasional prolonged menstrual periods. A total hysterectomy was performed, and at the time of operation she had been menstruating for 13 days; histologically the uterus showed a normal proliferative endometrium. Fluid was obtained from a large cyst in the left ovary. Histological examination of the cyst revealed normal granulosa and theca interna layers.

Case 8.—A total hysterectomy was performed for severe menorrhagia 24 days after the commencement of her last menstrual period. Histologically the uterus appeared normal, and it was lined by a late secretory endometrium. The fluid was obtained from a cyst in the left ovary.

Case 9.—Aged 29. This patient had a history of continuous vaginal bleeding for six weeks, and at laparotomy an unruptured ectopic pregnancy was discovered in the right fallopian tube. Her last menstrual period had occurred 51 days prior to the operation. Fluid was obtained from several small follicles in the right ovary.

Case 10.—Aged 28. A laparotomy was performed for sterilization by tubal ligation 11 days after the beginning of the last menstrual period. A complete Graafian follicle 1.5 cm. in diameter was removed intact from the right ovary. Fluid was subsequently aspirated from the excised follicle.

Case 11.—Aged 34. This patient complained of abdominal pain, and a laparotomy was performed 14 days after the beginning of the last menstrual period. Fluid was obtained from a large follicular cyst in the right ovary.

Case 12.—Aged 35. A total hysterectomy was performed for severe dysmenorrhoea two days after the commencement of the last menstrual period. Both the uterus and the ovaries appeared normal. Fluid was obtained from numerous small follicles by multiple incisions in both ovaries.

Results

The results of the steroid assays on the samples of cyst fluid are shown in the Table. It was necessary to combine the material from Cases 4 and 5 in order to obtain sufficient fluid to assay.

Concentration of Steroids in the Fluid from Human Ovarian Cysts and Follicles

Case No.	Diagnosis	Vol. of Fluid (ml.)	Progesterone (μg./100 ml.)	17α-Hydroxy-progesterone (μg./100 ml.)	Andro-stenedione (μg./100 ml.)	Oestrone (μg./100 ml.)	Oestradiol-17β (μg./100 ml.)
1	Stein–Leventhal	2·5	<10	32	88	<2	<2
2	,,	1·4	7	36	196	<2	<2
3	,,	3·2	13	39	156	<2	<2
4 and 5	,,	2·6	<12	23	134	<2	<2
6	Menorrhagia	2·8	109	55	32	7	156
7	,,	25·0	54	31	5	<1	36
8	,,	8·5	9	13	19	2	24
9	Ectopic pregnancy	7·6	310	58	23	<1	4
10	Normal	2·0	95	85	78	68	70
11	Ovarian cyst	17·0	47	36	38	2	22
12	Dysmenorrhoea	1·7	15	21	35	18	44

The most striking finding in the patients with Stein–Leventhal syndrome was the very high concentration of androstenedione present, coupled with a complete absence of detectable amounts of oestradiol-17β or oestrone. In the control group of patients, on the other hand, the levels of androstenedione are significantly lower, and oestradiol-17β was detected in every sample. These oestradiol values are within the range of those reported by Granjon *et al.* (1958), Zander *et al.* (1959), and Smith (1960) for normal and cystic follicles. However, most of the oestrone values seem to be somewhat lower than the ones found by these authors.

The results in the Table therefore strongly suggest that in the Stein–Leventhal syndrome there is a defect in the conversion of androstenedione to oestradiol-17β within the cystic follicles. The resultant build-up of androstenedione could possibly account for the clinical signs of virilism in these cases. However, although androstenedione is a potent androgen when administered locally, it has only a very weak androgenic activity when administered systemically (Dorfman and Shipley, 1956; Mann *et al.*, 1960).

It can also be seen from the Table that some of the control patients had very high concentrations of progesterone in their cyst fluid. In some instances—for example, Case 9—this may have been due to the fact that luteinization changes were taking place in the follicles (Short, 1961).

In addition to steroids listed in the Table, an attempt was made to identify a number of other compounds. Zander *et al.* (1958) reported the presence of 20ξ-hydroxypregn-4-en-3-one in human ovaries, but there was no evidence of either the 20α or 20β epimer in any of the samples assayed in this study (<1μg./sample). This is in agreement with observations on the mare's ovary (Short, 1961), where 20α-hydroxypregn-4-en-3-one was found in the corpora lutea but not in the follicular fluid.

Zander *et al.* (1959) were unable to identify any oestriol in human ovaries, although Smith (1960) reported finding large amounts (24 μg./100 ml.) in a pool of secretory-phase follicular fluid; more recently, however, Ryan and Smith (1961a, 1961b) failed to demonstrate any *in vitro* conversion of acetate or progesterone to oestriol by the linings of human follicular cysts. In the present study, oestriol was not detected in any of the 12 samples assayed (<0.1 μg./sample).

With the recent identification of dehydro*epi*androsterone in testicular tissue (Neher and Wettstein, 1960), it seemed possible that this androgen might also be produced by the ovary; however, it was not detected in any instance in the present study (<2 μg./sample).

Since the ovary is capable of producing androstenedione, it is also possible that it could produce testosterone. There is some evidence for testosterone production by pathological human ovarian tissue *in vitro* (O'Donnell and McCaig, 1959; Mills *et al.*, 1959), but as yet testosterone has not been isolated from human ovaries *in vivo*. In the paper chromatographic system used in the present study, it is not possible to separate testosterone from 17α-hydroxyprogesterone. Therefore the 17α-hydroxyprogesterone eluates from Cases 3, 4, and 5 were pooled, treated with acetic anhydride and pyridine, and rechromatographed. No testosterone acetate could be detected, indicating that there must have been less than 1 μg. of testosterone in the original pooled sample. The 17α-hydroxyprogesterone eluates of Cases 6, 7, 8, and 9 were treated in the same way, with similar negative results. This is in agreement with the findings in another study (Short, unpublished observations) in which <0.1 μg. of testosterone was present in 6.5 μg. of 17α-hydroxyprogesterone isolated from a pool of human ovarian cyst fluid.

A number of other steroids have been isolated from the follicular fluid of the mare—namely *epi*testosterone (Short, 1960a), 6α-hydroxyoestradiol-17β (Bush *et al.*, 1960), and 19-norandrostenedione (Short, 1960b); however, none of these steroids was detected in this study (<1 μg./sample). No attempt was made to look for 19-hydroxyandrostenedione, the postulated intermediate in the conversion of androstenedione to oestrone (Meyer, 1955; Ryan, 1959), since this steroid has never been detected in large pools of human, equine, or bovine follicular fluid (Short, 1960a, 1960b, and unpublished observations).

Discussion

In interpreting the results of this study it has been assumed that the steroid concentrations in follicular fluid are a valid index of the *relative* amounts of each hormone secreted by the cells lining the follicle (Short, 1961). However, it is important to remember that such estimations do not necessarily provide any information about the secretion rates of the hormones concerned. Thus, while the results presented here strongly suggest that there is a defect in steroid biosynthesis in the ovary, resulting in a build-up of androstenedione and a decreased production of oestrogens, it is not possible to determine the quantitative significance of the defect.

Studies of endometrial histology (Stein, 1955; Leventhal, 1958) and urinary oestrogen excretion (Evans and Riley, 1960; Shearman *et al.*, 1961) in the Stein–Leventhal syndrome have indicated that oestrogens are being produced in amounts comparable to those found in the middle of the proliferative phase of the normal menstrual cycle. In view of the fact that the theca interna cells are probably responsible for oestrogen synthesis in the ovary (Brambell, 1956; Falck, 1959; Pinkerton, 1959), one might have expected the hyperthecosis found in the Stein–Leventhal syndrome to result in a greatly increased production of oestrogens. The fact that this is not so lends some support to the concept of a block to oestrogen synthesis in these thecal cells.

The residual oestrogens that are produced could be coming from the remaining normal tissue in the ovary; or it may be that the defect is not an absolute one, and that even the cystic follicles can produce small amounts of oestrogen. Evans and Riley (1960) briefly reported finding oestrogenic activity in some Stein–Leventhal follicles, while none was detected in others. It should also be remembered that the adrenals are apparently capable of producing at least as much oestrogen as the ovaries (Brown *et al.*, 1959), and there is evidence (Gallagher *et al.*, 1958; Prunty *et al.*, 1958; Shearman *et al.*, 1961) to suggest that the adrenals may be hyperactive in the Stein–Leventhal syndrome.

From the results presented in this study it is not possible to locate the exact site in the biosynthetic sequence at which the block occurs, except that it appears to be somewhere between androstenedione and oestrone. It is generally believed that androstenedione is converted to oestrone via 19-hydroxyandrostenedione (Meyer, 1955; Ryan, 1959); hence the defect could possibly be in the 19-hydroxylating enzyme system. It is well known that similar hydroxylation disorders occur in the adrenal cortex in congenital adrenal hyperplasia, when the 11- or 21-hydroxylating enzyme systems appear to be at fault.

It has been postulated by Hollander and Hollander (1958), on the basis of *in vitro* experiments with dog ovaries, that the conversion of C_{19} steroids like androstenedione to oestrogens is a rate-limiting reaction, which is under the control of follicle-stimulating hormone. If this theory is correct, then the defect in

the Stein–Leventhal ovaries could result from a decreased secretion of follicle-stimulating hormone by the pituitary. However, more recent *in vivo* evidence (Short, 1961) strongly suggests that there are no such rate-limiting reactions under gonadotrophic control in the conversion of androstenedione to oestradiol-17β by the ovary.

One of the most puzzling features of the Stein–Leventhal syndrome has been the success of such a wide variety of surgical procedures for its treatment; the only factor they apparently have in common is trauma to the ovary. It is known that, in some animals, artificial rupture of large follicles will bring about luteinization changes indistinguishable from those that normally follow ovulation (Harrison, 1946). The essential biochemical difference between a follicle and a corpus luteum seems to be that luteal tissue is relatively deficient in the enzyme systems responsible for hydroxylation at position 17, side-chain cleavage, and aromatization. Thus the corpus luteum is forced to produce mainly progesterone, and little 17α-hydroxyprogesterone, androstenedione, or oestrogens are formed (Short, 1961, and unpublished observations). It therefore seems possible that the trauma involved in the surgical correction of Stein–Leventhal ovaries could provide the stimulus for luteinization of the defective cystic follicles. Many of the thecal cells would then regress in the normal way, and the granulosa cells would luteinize and start secreting progesterone.

Summary

An analysis of the steroids present in cyst fluid from the ovaries of five patients with the Stein–Leventhal syndrome revealed a very high concentration of androstenedione, and no detectable amounts of oestradiol-17β or oestrone. In seven control patients, on the other hand, in whom normal or cystic follicles were an incidental finding at laparotomy, the concentrations of androstenedione were significantly lower, and oestradiol-17β was detected in every instance.

On the basis of this evidence it is therefore postulated that in the Stein–Leventhal syndrome there is a defect in the biosynthesis of oestrogens within the cystic follicles. This defect takes the form of a block in the conversion of androstenedione to oestrogens; the resultant increase in androstenedione production could possibly account for the virilism seen in some patients. A tentative explanation is also offered for the success of such a wide variety of non-specific surgical procedures in curing the condition.

We are grateful to Dr. T. Mann, F.R.S., and Professor F. T. G. Prunty for their help and advice during the course of this study. We thank Mr. S. L. Barron and Mr. G. W. Garland for operating on the Stein–Leventhal patients; and Mr. J. S. Hesketh, Dr. A. Klopper, and Mr. C. Macnaughton for providing the follicular fluid from the control group of patients. Dr. R. Vaughan-Jones and Dr. J. L. Pinniger kindly carried out the histological examinations for us. We are indebted to Dr. J. S. M. Hutchinson for the gonadotrophin assays, and to Dr. R. V. Brooks for the routine urinary steroid determinations.

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The Hong Kong Government recently accepted a report by Dr. L. T. HILLIARD, formerly consultant psychiatrist and superintendent of the Fountain Hospital, London, as a guide to policy for dealing with the problem of mental deficiency in the Crown Colony. Dr. Hilliard went to Hong Kong last year to examine the problem of mental deficiency there and to advise on measures for dealing with the problem. The Acting Colonial Secretary has told the Hong Kong Legislative Council that it was proposed to proceed in three different but interrelated fields. Under the Medical Department would come the diagnosis of all mental defectives and the provision of separate hospital accommodation for severe-grade mental defectives. The provision of residential and day-training institutions for medium-grade mentally defective children and adults would be the responsibility of the Social Welfare Department. The Education Department would deal with the provision of special facilities for teaching minor-grade mental-defective children. In his report Dr. Hilliard said most of the existing tests of intelligence were inappropriate and inaccurate when applied to races or countries for which they had not been devised. He emphasized that it would be useful if a clinical psychometrist undertook some research into this matter in Hong Kong, and he suggested that this might be provided through Unesco.

SPECIFICITY OF INTERFERON

BY

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Cells treated with heat-inactivated influenza virus have the property of interfering with the growth of other viruses. Isaacs and Lindenmann (1957) gave the name "interferon" to the substance responsible for this interference. Substances with similar properties have since been found in many virus–host cell systems (Ho and Enders, 1959). There is some evidence (Isaacs and Hitchcock, 1960) that interferon may be in part responsible for recovery from virus infection. Interferon is non-specific in its action against viruses, that produced by influenza virus, for example, having been shown to be active against members of the myxovirus, enterovirus, pox virus, and arbor virus groups.

Burke (1961) has shown that interferon is a protein of molecular weight approximately 62,000 and that it is either non-antigenic or only poorly so. It is relatively stable to heat and changes in *p*H. It is active on virus-infected cells not only *in vitro* but also *in vivo*, as has been shown for vaccinia virus infections of the skin of rabbits (Lindenmann *et al.*, 1957; Isaacs and Westwood, 1959) and of the eyes of rabbits (Cantell and Tommila, 1960), and for Bunyamwera virus in mice (Hitchcock and Isaacs, 1960). Interferon production *in vivo* has been shown to occur also in mice infected by influenza virus (Isaacs and Hitchcock, 1960) and for vaccinia infection of rabbits' skin (Nagano and Kojima, 1958). It thus has physical and biological properties that make it of potential value as a broad-spectrum viral antibiotic.

However, it has been found that interferon prepared from cells of the species of animal used in the test system is more effective than interferon prepared in a foreign species. This has been shown to be the case both *in vivo* and *in vitro* (Isaacs and Westwood, 1959; Sutton and Tyrrell, 1961). It would clearly be preferable on the grounds of safety and economy to use for man interferon prepared from non-human, and preferably non-primate, cells. It was therefore decided to reinvestigate how interferon preparations made in various different types of cell affected the development of vaccinial lesions in animals.

Methods

Chick interferon was prepared as previously described (Andrews and Dudgeon, 1961). Human-amnion, monkey-kidney (rhesus and cynomolgus), and rabbit-kidney interferons were made by infecting monolayer cell-cultures with the Melbourne strain of influenza virus inactivated by ultra-violet light, as described for the preparation of chick interferon. After three hours at 37° C. the virus was replaced by Earle's saline, and the final culture was harvested after 24 hours at 37° C. Control preparations were similarly made, but without infecting the cells with irradiated influenza virus. The possibility that interferon was produced in the control cell-cultures by a latent virus producing no degeneration of the cultures was not excluded, but none appeared to have been present to any great extent, as judged by the results. (We have previously observed partial inhibition of vaccinia in the rabbit's skin with one control preparation. The inhibition was intermediate between that produced by a known sample of interferon and the "unprotected" vaccinial control.) Interferon-containing solutions were dialysed against citrate buffer at *p*H 2 for 24 hours and then adjusted to *p*H 7.2, as recommended by Isaacs and Burke (1958).

FIG. 1

FIG. 2

FIG. 1.—Skin of rabbit showing sites of injection of interferon and vaccinial lesions. A, Chick interferon (M 1). B, Chick interferon control. C, Monkey interferon control. D, Rabbit interferon control. E, Medium 199. F, Calf interferon. G, Chick interferon (G 10). H, Monkey interferon (C 9). I, Rabbit interferon (G 12). J, Vaccinia control.

FIG. 2.—Skin of cynomolgus monkey showing sites of injection of interferon and vaccinial lesions. A, Chick interferon (G 5). B, Chick interferon (G 29). C, Cynomolgus monkey interferon (G 21). D, Rhesus-monkey interferon (G 32). E, Rabbit interferon (G 12). F, Vaccinia control.

Concentration of Interferon.—Some interferon preparations were concentrated approximately 10 times. This was achieved either by freeze-drying or by osmodialysis with 40% polyethylene glycol ("carbowax" 20,000 M or 4,000 M). Polyethylene glycol, especially the material of average molecular weight 4,000, diffused through the dialysis bags into the interferon, but did not invalidate its measurement either *in vitro* or *in vivo*.

Animal Experiments

Three experiments, each on six rabbits, were carried out. Interferon (0.1 ml.) was injected intradermally into the depilated flanks of the rabbits at five or six sites on each side. Vaccinia virus (20% suspension of infected chick chorio-allantoic membranes) was used as a challenge virus. Either immediately or 24 hours later, 0.1 ml. was inoculated at the same sites. The lesions were examined daily, and the diameter of the erythema was measured in millimetres. The mean diameters for six rabbits recorded on the stated (usually sixth) day after challenge with vaccinia virus are given in the tables. Necrosis and subsequent scab formation were recorded on an arbitrary scale, + indicating for each rabbit the usual degree of necrosis seen in untreated areas of rabbit skin challenged with vaccinia. There was a slight variation in susceptibility to vaccinia from rabbit to rabbit.

The single experiment with a cynomolgus monkey was performed in a similar manner, except that the challenge virus was a 50% suspension of chick chorio-allantoic membranes. The rhesus monkeys available were found to be relatively resistant to vaccinia given intradermally.

Results

In the first experiment, as shown in Table I and also in Fig. 1, it was found that the rabbit-kidney interferon and the chick interferon (G 10) greatly reduced the area of erythema and oedema when given 24 hours before challenge. The rabbit interferon completely suppressed necrosis in all six rabbits, and the other interferons restricted the necrosis to two out of the six rabbits, compared with the vaccinia controls, in which necrosis developed in five out of six. The interferon controls produced a slight but perceptible protective effect.

The results of the second experiment are shown in Table II. All the interferon preparations given 24 hours before challenge suppressed necrosis, and the rabbit-kidney interferon was the most effective preparation. The cynomolgus-monkey interferon and one batch of chick interferon (G 29C), and also the homologous interferon, markedly both reduced the area of erythema and suppressed necrosis when given 24 hours before

TABLE I.—*Effect at 6 Days of Species of Origin of Interferon on Vaccinia Virus Infections of the Skin of Rabbits*

	Species of Origin of Interferon given 24 Hours before Challenge						Controls given 24 Hours before Challenge			
	Chick M 1	Chick G 10	Calf	Monkey[1] C 9	Rabbit[2] G 12	None	Medium 199	Chick	Monkey[1]	Rabbit
Necrosis. Each + represents a necrotic lesion in one rabbit	++	++	++	++	0	+++++	+++++	++	+++	++
Diameter of lesions (mm.)	5	2	6	13	3·5	12·5	12	7	10	8

[1] Cynomolgus monkey. [2] Concentrated ×5 by polyethylene glycol.

TABLE II.—*Effect at 6 Days of Time of Administration and Species of Origin of Interferon on Vaccinial Lesions*

		Species of Origin of Interferon				
		Control	Chick[1] G 5	Chick[2] G 29C	Rabbit[3] G 12	Monkey[4] G 21B
Interferon given 24 hours before challenge	Necrosis	++++++	0	0	0	0
	Diameter of lesions (mm.)	13·3	12	4·2	2·4	3·6
Interferon and vaccinia given simultaneously	Necrosis	++++++	+++++++	++++	0	0
	Diameter of lesions (mm.)	15·6	18	6·1	5·7	8·1

[1] Concentrated ×10 by freeze-drying. [2] Concentrated ×10 by polyethylene glycol. [3] Concentrated ×5 by polyethylene glycol. [4] Cynomolgus monkey.

TABLE III.—*Effect at 6 Days of Time of Administration and Species of Origin of Interferon on Vaccinial Lesions*

		Species of Origin of Interferon					
		Control	Chick G 10	Monkey[1] G 32	Monkey[2] G 21B	Human Amnion G 35	Rabbit G 12
Interferon given 24 hours before challenge	Necrosis	++++	0	0	0	0	0
	Diameter of lesions (mm.)	18·8	5·1	5·1	4·1	3·4	0
Interferon and vaccinia given simultaneously	Necrosis	++++	++	++++	+	++	0
	Diameter of lesions (mm.)	20·1	17·6	20·8	11·7	17·4	4·3

[1] Rhesus monkey. [2] Cynomolgus monkey.

TABLE IV.—*Effect of Species of Origin of Interferon on Vaccinial Virus Infections of the Skin of a Cynomolgus Monkey*

		Species of Origin of Interferon given 24 Hours before Challenge					
		Control	Chick[1] G 5	Chick[2] G 29C	Monkey[3] G 21	Monkey[4] G 32	Rabbit[5] G 12
8 days	Lesion	Pustule	—	Pustule	—	—	Pustule
	Diameter of erythema (mm.)	14	0	12	0	0	14
10 ,,	Lesion	Erythema with central necrosis and large scab	—	Erythema with central necrosis and large scab	—	Erythema with small scab	Erythema with central necrosis and large scab
	Diameter of erythema (mm.)	11	0	12	0	6	12

[1] Concentrated ×10 by freeze-drying. [2] Concentrated ×10 by polyethylene glycol. [3] Cynomolgus monkey. [4] Rhesus monkey. [5] Concentrated ×5 by polyethylene glycol.

challenge. The rabbit and cynomolgus-monkey interferons were also effective when given simultaneously with the vaccinia virus.

The third experiment showed that chick, rhesus, cynomolgus, human-amnion, and rabbit interferons were all active in suppressing the lesions when given 24 hours before challenge (Table III). Necrosis was observed only in the vaccinia controls. When the interferons were given at the same time as the challenge the homologous interferon gave good and the cynomolgus interferon slight protection.

Observations on the development and subsequent remission of the lesions confirmed these findings.

The results of the single experiment with a cynomolgus monkey are shown in Table IV, and also in Fig. 2, where it will be seen that the homologous interferon and the heterologous chick interferon (G 5) were highly effective in inhibiting vaccinial lesions. The rhesus-monkey interferon was rather less active.

Attention is called to the fact that the chick interferon (G 5) was found to be minimally active in rabbits (Table II) and that the rabbit (G 12) and the chick interferons (G 29C) were active in rabbits but inactive in the cynomolgus monkey.

Discussion

Isaacs and Westwood (1959) have described the superiority of rabbit over chick interferon in the inhibition of vaccinial lesions in the rabbit skin. Sutton and Tyrrell (1961) have shown in tissue-culture systems that interferon prepared in homologous cells is more effective than that prepared in heterologous cells. They also found that this species specificity in the action of interferon was not absolute, and, in particular, that rhesus-monkey interferon was the one most active on heterologous cells, including human cells. The work described here confirms these observations to some extent. Thus the rabbit and monkey (cynomolgus) interferons were most active in rabbits and a monkey, respectively. However, significant inhibition of vaccinial lesions in the skin was produced by some preparations of heterologous interferon. This observation could be important if interferon proves effective in human virus infections and might open the way to use of non-human cells in preparing interferon intended for therapy in human subjects. At present the evidence adduced here, like that of Sutton and Tyrrell (1961), suggests that monkey cells are a source of interferon that could reasonably be used in experimental work on man, but the choice of the best cell for producing interferon for use in man must await the results of further tests and clinical trials.

Summary

Interferon prepared from various species of cells has been found to inhibit the development of vaccinial lesions in the skins of rabbits and a monkey. Though the interferon prepared in homologous species of cells has the greatest effects, significant inhibition was produced by some interferons prepared from heterologous cells.

I thank Dr. J. A. Dudgeon for his advice and encouragement, and Mr. G. T. Hawkins and Mrs. E. M. Kemp for their able technical assistance. The sample of chick interferon supplied by Dr. A. Isaacs, of the National Institute for Medical Research, and one of calf interferon supplied by Dr. N. Finter, of Imperial Chemical Industries, are gratefully acknowledged.

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EPIDEMIOLOGY OF ACUTE INTUSSUSCEPTION

BY

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The north-east region of Scotland is a very suitable area in which to carry out incidence studies. About 90% of all the surgical emergencies occurring in the population of 425,000 are dealt with in the Aberdeen general and special hospitals. When the fringe counties of Kincardineshire and Morayshire are excluded the percentage of referrals approaches 100%. This is especially true of an acute abdominal condition such as intussusception. Several detailed studies on the incidence of intussusception have been carried out in densely populated and industrial areas of Britain (Morrison and Court, 1948; MacMahon, 1955; Court and Knox, 1959; Smith, 1960), but little has been known about its incidence in a less densely populated and mainly rural area. The present investigation was designed to provide such information.

The Investigation

Clinical Material.—The case records of all acute intussusceptions occurring in Aberdeen City, Aberdeenshire, and Banffshire during the years 1950–9 were studied. There were 145 cases, 140 being of the so-called idiopathic type. All except three had been treated at the Royal Aberdeen Hospital for Sick Children; smaller peripheral hospitals were visited to ensure that no cases were missed. From the data collected the incidence in the population at risk, the seasonal incidence, the age-and-sex distribution, and the family histories of the children affected were determined.

Incidence

During the decade under review there were 66,144 live births in the three areas designated above. The 145 intussusceptions occurring during this period therefore give an overall incidence of 2.19 per 1,000 live births (Table I). When the incidences in the city and in the two county areas are compared, it is found that the incidence is greater in the rural districts (2.55 per 1,000 births compared with 1.81 in the city). This difference is statistically significant ($\chi^2=4,131$; D.F. 1; $0.02<P<0.05$). The permanent address of the mother has been

used in classifying the live births; this eliminates the possibility of maternal migration to the city at full term giving an excessive number of births within the city and so an artificially low incidence of intussusception. Comparable figures for other cities are given in Table II.

TABLE I.—*Incidence per 1,000 Live Births in City and Rural Areas of N.E. Scotland*

	Cases	Live Births	Incidence per 1,000 Live Births
Aberdeen	58	32,033	1·81
Aberdeenshire	68	25,484	2·66
Banffshire	19	8,627	2·20
	145	66,144	2·19

TABLE II.—*Incidence per 1,000 Live Births in British Cities*

Newcastle	4·3	Edinburgh	1·57
Birmingham	1·49	Aberdeen	1·81

Seasonal Incidence.—It has often been suggested that intussusceptions may be more common at certain times than at others. In the present series both the numbers of cases occurring in each of the months of the year (monthly incidence, Fig. 1) and the number of months with different numbers of cases ("run" analysis, Fig. 2) have been calculated for the 10-year period. The monthly incidence shows that intussusception occurs slightly more often in spring and autumn, but the difference between the various months is not great, ranging from 7 to 18. The run analysis, to see if intussusception took place in small epidemics, was inconclusive, there being little systematic disagreement between the observed data and the theoretical Poisson distribution. When, to test for clumping of cases, the observed variability is compared with the value expected if the cases occurred at random, the difference is not significant ($\chi^2=123$; D.F.$=119$; $P>0.1$) when periods of one month are studied—that is, there is no evidence of clumping in months. There is, however, some indication of grouping of cases over periods of a few months, particularly in 1954 and 1955. A test of the heterogeneity of the number of cases occurring in each of the 20 six-month periods reviewed gave a χ^2 of 30.4 (D.F.$=19$; $0.02<P<0.05$). For the 10 twelve-month periods $\chi^2=18$ (D.F.$=9$; $0.02<P<0.05$). There is therefore some evidence of non-randomness in the occurrence of intussusception over longer periods.

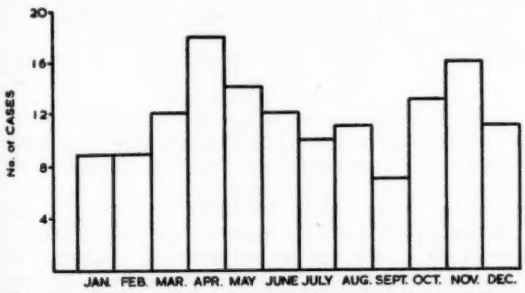

FIG. 1.—Monthly incidence of acute intussusception during the 10-year period 1950–9.

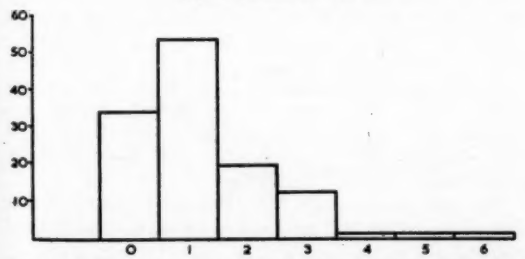

FIG. 2.—Monthly "run" analysis, showing the number of months (ordinate) in which various numbers of cases of intussusception (abscissa) were admitted. Average per month = 1.2.

Age and Sex Distribution

In recording the age of the children affected the actual age at the time of admission has been used, not the age next birthday. All the children are aged 6 years or under, apart from one boy of 11 years (Fig. 3). Only 77 patients, representing 53% of the total, are less than 1 year of age, which is a much smaller percentage than that given by other authors (Table III).

In this series of 145 patients, 60% are males—a male preponderance rather lower than that usually found (Table IV). In infants under the age of 9 months MacMahon (1955) found no sex difference, but in the present series there is still a slight male preponderance, 55%.

In females 56% of intussusceptions occur before the age of 1 year, while in males 50% are below that age. Wilcoxon's test (Siegel, 1956) was applied to assess the significance of the sex differential in the male and female groups. The calculated probability of the differential occurring by chance is less than 1 in 100; the earlier onset of intussusception in girls as compared with boys is therefore highly significant and may indicate a difference in the inherited susceptibility to the condition in the two sexes. In the rural areas 63% of the patients were males, while from the city only 55% were males.

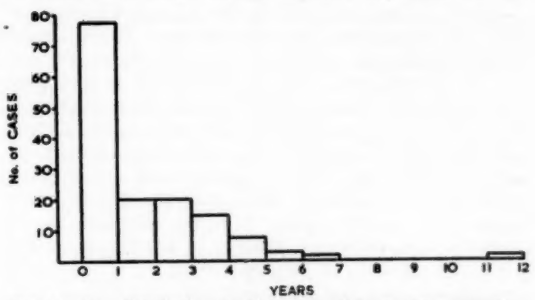

FIG. 3.—Age distribution in 145 cases of acute intussusception.

TABLE III.—*Percentage of Patients Below 1 Year of Age in Six British Cities*

Author	Area	Below 1 Year
Kyle (1954)	Belfast	71%
Perrin and Lindsay (1921)	London	70%
Stewart (1960)	Edinburgh	69%
MacMahon (1955)	Birmingham	65%
Strang (1959)	Glasgow	63%
Present series	Aberdeen	53%

TABLE IV.—*Sex Ratio in Ten Different Areas*

Author	Area	Percentage Male
Stewart (1960)	Edinburgh	69
Fitzwilliam (1908)	U.K.	68
Koch and Oerum (1912)	Denmark	68
Kyle (1954)	Belfast	66
MacMahon (1955)	Birmingham	65
Hipsley (1926)	Australia	64
Strang (1959)	Glasgow	63
Clark *et al.* (1959)	Canada	60
Present series	Aberdeen	60
Morrison and Court (1948)	Newcastle	55

Family History

In this series of 145 cases there are two families (one out of 72 families) in which another sibling or parent has had an intussusception. MacMahon (1955) calculated that the eight affected families in his series of 396 cases (one out of 50) represented a familial incidence 40 times greater than would have been expected by chance. Although less marked, the familial incidence in the present series still is much greater than can be accounted for by a random occurrence of intussusception, and the figure has been derived simply from a review of case records. Detailed field inquiries, as carried out by MacMahon, might well reveal more affected families. In one of the two families noted the father, a general practitioner, had suffered from a recurrence of his intussusception, and a similar double misfortune befell his son.

Discussion

The incidence of acute intussusception in the City of Aberdeen (1.81 per 1,000 live births) is only slightly greater than that in Birmingham and Edinburgh. The accuracy of ascertainment of cases is probably the same in all three regions and in Newcastle, since the reported incidence of congenital pyloric stenosis (approximately 3 per 1,000 live births) is the same in each of them (Davison, 1946 ; MacMahon *et al.*, 1951 ; McLean, 1956 ; Smith, 1960). The significantly greater incidence in the rural areas is unexplained, but it is still little more than half the Newcastle figure.

Intussusception may result from a congenital predisposition being triggered off by an acquired agent. The male preponderance and the increased incidence of intussusception among relatives may be accounted for by some inherited predisposition or abnormality such as excessive quantity or reactivity of alimentary lymphoid tissue. It is difficult to account for them by any other theory. At the same time an acquired agent seems the most likely explanation for intussusception occurring in small outbreaks lasting a few months. The nature of the acquired agent is unknown, and it may not be pathogenic in ordinary infants. The unusually large size of the mesenteric lymph nodes suggests that they may react vigorously. No known bacterium has been found blameworthy ; information is being collected about adenoviruses to determine whether or not they play any part in the aetiology of intussusception.

The increased incidence in the rural areas is not fully explained by either part of this suggested dual aetiology. Inbreedings could increase a congenital predisposition. On the other hand, failure of the infant to become immunized either passively or actively at a very early stage of its development to a relatively innocuous external agent such as an adenovirus may render it more susceptible to that agent at the age of a few months.

Summary

The incidence of acute intussusception and the age-and-sex distribution and family histories of the 145 patients seen in North-east Scotland from 1950 to 1959 have been determined.

The overall incidence is 2.19 per 1,000 live births ; the incidence is significantly greater in the rural area than in the City of Aberdeen.

The male preponderance is less marked than in other regions, but the sex differential is still highly significant.

When analysed for periods of six and twelve months, intussusception occurs in a non-random manner.

These findings suggest that acute intussusception results from a congenital predisposition being triggered off by an acquired agent, possibly an adenovirus.

We thank the medical staff of the Royal Aberdeen Hospital for Sick Children for permission to carry out this study, and Professor E. M. Backett and Dr. R. D. Weir, of the Department of Social Medicine, University of Aberdeen, for their advice. We are indebted to Dr. W. Brass, of the Department of Statistics, for his help in performing the statistical analyses.

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TWO INCIDENTS OF TUBERCULOUS INFECTION BY MILK FROM ATTESTED HERDS

PUBLIC HEALTH AND CLINICAL ASPECTS

BY

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This report describes two recent incidents where tuberculous infection occurring in children was apparently related to the consumption of milk from attested herds.

First Incident

In July, 1959, a routine tuberculin test of an attested dairy herd in Oxfordshire revealed six reactor cows. These animals were removed and slaughtered, and on post-mortem examination one animal was found to have a tuberculous udder. The herd was retested in September, 1959, when 19 animals were found to be positive reactors. These animals, together with a few doubtful reactors, were slaughtered, the result being the destruction of the entire milking herd. The cause of the breakdown in the herd was not established, but it was suggested that a cow which had been sold off the farm to a knacker, prior to July, 1959, may have been the originator of the herd infection.

The bulk of the milk from this herd had been sent daily for pasteurization before retail to the general public.

In November, 1959, a general practitioner informed the medical officer of health for Oxfordshire that a girl

aged 5 years, living in one of the farm cottages, had developed erythema nodosum and that her sister, aged 7 years, reacted positively to a 1:1,000 tuberculin test. These girls came from a family which had received a daily supply of untreated milk from the herd in question. The other members of the family—mother, father, and a third sister—were seen at the chest clinic. All had positive tuberculin tests (Heaf type). Their chest *x*-ray films were satisfactory and they were all well and free from symptoms.

Inquiries revealed that a second family, living in an adjoining farm cottage, had also received a regular supply of raw milk. The members of this family were examined at the chest clinic. The mother, father, and two sons aged 2 and 4 years had positive Heaf tests, but the baby aged 6 months, who had been fed on national dried milk, was Heaf-negative. Members of the farmer's family, who were the only others consuming the raw milk, gave the following Heaf results: mother was negative, and father and two sons aged 15 and 16 years were all positive.

Because of the clear-cut history of recent exposure to infection the positive tuberculin reactors were each given a six-months course of antituberculous chemoprophylaxis. The adults received isoniazid 300 mg. daily and sodium P.A.S. 12 g. daily. The children received doses appropriate to their age and weight; these varied between 2 and 4 g. of P.A.S. daily, and between 50 and 100 mg. of isoniazid daily. No toxic reactions occurred in the above group.

This incident had limited consequences in that only three families were regularly supplied with untreated milk from the affected herd, but it did serve to alert both the veterinary and the public health authorities to the possibility of tuberculous infection occurring in attested herds with consequent danger to the consumers of raw milk.

Second Incident

In December, 1959, the medical officer of health for Oxfordshire was informed by the divisional veterinary officer that a cow originating from attested premises in the county had subsequently been slaughtered in London and had been found to be affected by tuberculosis. The hind quarters and offal were condemned, but there was no macroscopic evidence of tuberculosis of the udder.

The origin of the animal was a self-contained Friesian herd which had been attested since 1947. The last positive reactor had been found in 1951. The herd was last tested in June, 1959, when all the animals, including the one in question, were found to be negative.

The history of the animal revealed that she had suffered from clinical mastitis in one-quarter of the udder in September, 1959. None of her milk was thenceforward used for human consumption, but milk from the apparently healthy quarters of the udder was fed to calves. As the mastitis did not clear up the cow was dried off and sold.

A herd tuberculin test was immediately carried out, and this revealed 35 positive reactors and 6 inconclusive reactors. The reactors comprised 1 bull, 12 cows, and 22 calves. Three of the calves were approximately 3 months old and 19 were 4 months old. All the calves under 3 months old and over 4 months old passed the test. None of the calves which had received milk from the three apparently healthy quarters of the udder reacted to the test.

The history and the result of the tests suggested that this cow had been excreting tubercle bacilli in her milk for about six weeks before the development of clinical evidence of mastitis in September, 1959.

All the reacting animals were slaughtered and post-mortem examination revealed glandular involvement in 18. Macroscopically affected lymphatic glands examined by the Ministry of Agriculture's laboratory at Weybridge were reported positive for tubercle bacilli which were typed as bovine strain.

It was ascertained that the bulk of the milk from the herd was sent for pasteurization, but that about 20 gallons (91 litres) of untreated milk were retailed daily in the adjoining village. A list of consumers was obtained and the general practitioners in the area were informed of the situation.

After consultation with the chest physician it was decided to tuberculin-test all children and young persons up to the age of 21 years who might have consumed the untreated milk. The consent of parents was obtained by house-to-house visitation by health visitors and tuberculin tests by the Heaf method were carried out early in January, 1960. The results are shown in Table I.

TABLE I.—*Result of Tuberculin Tests*

	No. Tested	Total No. of Tuberculin-positive Reactors			Total No. of Negative Reactors
		History of Previous Positive Reaction	History of B.C.G. Vaccination	No History of Positive Reaction or B.C.G.	
Pre-school	50	—	1	20	29
At school	92	3	13	42	34
Left ,,	18	—	9	4	5
Total ..	160	92			68

Of the 23 children who had had previous B.C.G. vaccination, 10 had strongly positive Heaf reactions (+++) or (++++), indicating very probably a superimposed infection.

All the positive reactors were examined at a series of special clinics held by the chest physicians. At the first examination two of the children, a boy aged 5 and a girl aged 13, were found to have unilateral enlargement of tonsillar lymph nodes. Of the 92 positive reactors, 85 accepted the offer of a prophylactic course of "pycamisan 33" according to the following dose schedule:

Age in Years	No. of Cachets Daily	Age in Years	No of Cachets Daily
Under 2	1	12 and under 14 ..	6
2 and under 4	2	14 and under 16 ..	8
4 and under 7	3	16 and over	9
7 and under 12 ..	4		

Each cachet of pycamisan 33 contained 1.5 g. of P.A.S. plus 33.3 mg. of isoniazid.

The girl aged 13, mentioned above, had some difficulty in taking the treatment because of nausea and loose bowel movements. Her treatment was interrupted and other forms of P.A.S. had to be tried. After three months the gland broke down to abscess formation and was operated on. The pus from the abscess contained acid-fast bacilli on the direct film, but, unfortunately, tubercle bacilli were not grown on culture and so the type of the bacillus was not determined. The boy aged 5 is progressing satisfactorily.

Twin girls aged 4 years who had been living in the village were traced to the area of another authority and on examination both were found to be tuberculin-positive; one child had enlarged cervical glands, and both had hilar enlargement on *x*-ray examination. Both

have since been admitted to a chest hospital. In each case gastric lavages were negative for tuberculosis on culture, but guinea-pig inoculation in both cases showed evidence of tuberculosis. Unfortunately, no positive cultures could be obtained from the guinea-pigs, and so the type of *Mycobacterium* is not known. On careful inquiry the only possible source of infection that could be discovered was the milk.

Of the 85 patients treated, several failed to take the full course because of various upsets. Table II gives a brief outline of the toxic effects noted.

TABLE II.—*Toxic Effects of Treatment*

Toxic Effects	No. of Patients	Ages	Result
Slight nausea	6	4–15	Treatment continued
Nausea	1	13	Missed "quite a few" cachets
	3	14–16	Stopped all treatment after 3 months
	2	14–18	Stopped all treatment after 1 month
Dermatitis	1	10	P.A.S. stopped. Isoniazid continued alone
Peripheral neuritis	1	17	Treatment stopped
Lassitude and evanescent rash	1	13	Treatment continued
Initial temporary depression	2	9–10	,, ,,
Jaundice and rash	1	5	Treatment stopped

Seven patients had to stop the treatment prematurely. Six patients admitted that they failed to take the drugs on occasions. Eight patients had some degree of upset but managed to complete the course.

It is almost certain the P.A.S. caused the toxic symptoms in 8 of the 85 cases treated, and in view of the investigation reported by Poole and Stradling (1960) one wonders how many more failed to take adequate dosage. Those workers noted that 6 of their 32 patients failed to take P.A.S. and that 9 others were so uncooperative in other ways that their intake of P.A.S. was suspect.

Discussion

Public Health Aspects

Incidents such as those recorded are, fortunately, not common nowadays. Hallo (1950) described infection among 100 young children and babies, the source of which proved to be milk from a farm with an attested herd, the last inspection of which had taken place six months previously when all the cows had given negative reactions to the tuberculin test. Subsequent testing of the herd revealed that 66% of the animals had become positive reactors. The source of infection of the herd could not be found. Faulds (1945) described a case of tuberculous meningitis in a child who had lived on a farm and who had received milk which was not heat-treated; the herd from which the milk came was apparently free from clinical tuberculosis at a routine examination. When this milk seemed by the history to be incriminated an examination of the animals revealed one cow with open tuberculosis of the udder, and a sample of the milk contained large numbers of tubercle bacilli. Wynne Griffith (1960) decribed an incident where the finding of positive tuberculin reactors in two young children was attributable to their drinking milk from a tuberculin-tested herd in which positive reactors had been discovered.

Recently the area eradication plan for attested herds has been extended to cover the whole country, and the incidents reported above may serve to warn against the false sense of security to be derived from the fact that future milk supplies will emanate entirely from attested herds. It is our experience that the designation of milk as tuberculin-tested cannot in the absence of pasteurization guarantee freedom from the presence of tubercle bacilli.

It is felt also that the notification of childhood tuberculosis warrants the most careful investigation into the source of the patient's milk, and where the latter has been consumed untreated the investigators should not be deterred from further search by the fact that the milk was designated as tuberculin-tested.

The prompt notification to the medical officer of health of tuberculous disease, in humans or in animals, is important. Our attention was drawn to the first incident as a result of an astute clinical observation by a general practitioner, who had noticed the relationship between the tuberculous infection in the herd and the infection in the children. The second incident demonstrates the value of close co-operation between the divisional veterinary officer of the Ministry of Agriculture and the county medical officer. In this case the divisional veterinary officer notified the county medical officer of the history of an animal slaughtered many miles outside the county, thus initiating the inquiry which is described above.

It may be useful to comment on the frequency with which attested herds are tuberculin-tested. At present the interval between tests is one year, although this may, in certain circumstances, be extended to two years. In addition, newcomers to the herd are tuberculin-tested as they arrive. Routine tuberculin-testing is carried out on the instructions of the Ministry of Agriculture. In both incidents reported above, a very rapid dissemination of infection took place in the herds once tuberculosis had been introduced. It might be advisable, therefore, if tuberculin tests could be carried out either at more frequent intervals or on each occasion when sickness in the herd cannot be clearly diagnosed as being non-tuberculous.

Clinical Aspects

Bacteriaemia is almost invariably present in primary infection. Guggenheim (1931) reported that he found abortive tuberculous haematogenous disseminations in 10% of 7,000 necropsies. The tuberculosis was noted as an "accidental finding," and so the percentage is a minimum one.

Foci may remain latent for many years and then produce bacillaemia and tuberculous lesions in various parts of the body, such as the lungs, meninges, bones and joints, and genito-urinary tract.

According to Kayne *et al.* (1948) malignant tuberculosis due to bovine tubercle bacilli is well known.

Davies (1960), reporting on the natural history of children exposed to mycotuberculosis, stated that between 1932 and 1950, 2,500 children were observed at the Brompton Hospital contact clinic and none had chemotherapy or B.C.G. vaccination: of 1,567 who were tuberculin-positive, 735 (47%) developed lesions. Among other things, he concludes that recent tuberculin conversion is an indication for treatment, especially during infancy and adolescence.

Many authors have shown that there is a risk of developing serious extrapulmonary tuberculous lesions after tuberculin conversion (Gedde-Dahl, 1948; Nissen Meyer, 1949, Anderson *et al.*, 1951; Thompson, 1952; Cammock and Miller, 1953; United States Public Health Service, 1957).

The United States Public Health Service (1957) reckon that isoniazid is 80% effective in preventing serious extrapulmonary complications. The follow-up is short, being at the most 30 months.

In the second outbreak mentioned, the bovine strain of tubercle bacilli was found in the slaughtered cows and, as no human source of infection could be found after an intensive search, it is reasonable to conclude that almost certainly the herd infection was due to a bovine source. One must also infer that the high percentage of tuberculin-positive reactors who had been consuming the herd milk, were also infected with the bovine strain of tubercle bacilli.

The dangers of recent and late disseminated tuberculous foci as described led to the decision that chemoprophylaxis should be given. From a long-term point of view nothing is known of the value of such prophylaxis, but the administration of isoniazid seems very worth while as it is an effective anti-tuberculous agent and as it diffuses into all tissues and fluids and into dense caseous lesions in high concentration (Barclay *et al.*, 1953).

To reduce the risk of resistant tubercle bacilli the isoniazid was combined with P.A.S. It would appear that children do not tolerate P.A.S. much better than adults and that preparations of the pycamisan type are not very suitable for mass prophylaxis.

Conclusion

The finding of a high percentage of positive tuberculin reactors among persons who had recently ingested untreated milk derived from tuberculin-positive cattle led to the decision that treatment should be offered to reduce the risk of subsequent disseminated tuberculosis.

The chemotherapy had untoward effects in an unexpectedly large number of children and so the dangers of inadequate treatment and dosage are very real. We believe that prophylactic treatment requires as careful supervision as routine therapy.

Close liaison between the Ministry of Agriculture, the medical officer of health, and the chest physician is of paramount importance. It is essential that the medical officer of health should be informed at once of any possible tuberculous infection which might directly or indirectly endanger the milk supply, so that appropriate public health measures may be instituted.

Our thanks are due to Dr. N. J. England, consultant chest physician, United Oxford Hospitals; to Dr. M. J. Pleydell, County Medical Officer of Health, Oxfordshire; and to Mr. J. G. Crowhurst, Divisional Veterinary Officer, Oxford, for advice and co-operation.

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THERAPEUTIC EFFECT, UTILIZATION, AND FATE OF INJECTED VITAMIN B_{12} IN MAN

A PRELIMINARY REPORT

BY

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During studies on the utilization of injected vitamin B_{12} in man, it was observed that an injection of 1,000 μg. of vitamin B_{12} given intramuscularly did not maintain the serum vitamin B_{12} level above the pre-injection level, or above the lower limit of normal, for much longer than an injection of 50 or 100 μg. given intramuscularly. It seemed likely that this might be due simply to the increased amount excreted after the larger injection. Detailed investigations, however, have shown that this is not the case and that the duration of effect of a large dose of vitamin B_{12} is much less than might be expected from the duration of effect of a small dose, even when allowance is made for the amounts excreted after injection.

Observations made on six patients which demonstrate this phenomenon clearly form the basis of this paper.

Patients, Materials, and Methods

The diagnosis of Addisonian pernicious anaemia was established in all patients on the basis of a macrocytic anaemia, megaloblastic bone-marrow, histamine-fast achlorhydria, low serum vitamin B_{12} level, and response to parenteral vitamin B_{12} only when they first came under observation. Absorption studies with radioactive vitamin B_{12} alone and with intrinsic factor were performed in all cases and confirmed the diagnosis. The patients were treated with parenteral vitamin B_{12} for several months, and then treatment was withheld and the serum vitamin B_{12} level estimated regularly. When the level fell to an arbitrary figure, usually about 140 $\mu\mu$g./ml., which is the lower limit of normal by the method used, the patient was given an injection of Co-58 vitamin B_{12}, 1,000 μg. 0.2 μc, or 100 μg. 0.2 μc, or 50 μg. 0.3 μc. The urine excreted in the subsequent 24 hours was collected, the radioactivity in an aliquot counted, and the total radioactivity calculated. This was taken to be a true measure of the amount of vitamin B_{12} excreted in the urine: the proof of this theory and the methods used are described in detail elsewhere (Adams, 1961).

After the first injection of Co-58 vitamin B_{12} the serum vitamin B_{12} level was estimated regularly, and when the level fell to about the original pre-injection level a second injection of Co-58 vitamin B_{12} was given and the cycle repeated. At the end of the period of observation all samples of serum obtained during the study were assayed in two different assay batches by a modification of the methods of Ross (1952) and of Hutner *et al.* (1956), using *Euglena gracilis* 3 strain as the test organism; the results presented here are based on the mean values of these two assays.

Results

Results in six cases are shown in graphical form in Figs. 1–6, and more detailed results from the same patients are set out in Tables I and II. In the figures the amount of vitamin B_{12} retained is shown in

parentheses after the amount injected. The utilization of the Co-58 vitamin B_{12} retained in the body was calculated from the formula:

(amount of vitamin B_{12} injected—amount of Co-58 vitamin B_{12} excreted) ÷ duration of effect in days.

TABLE I

Case No.	Pre-injection Serum Vitamin B_{12} Level ($\mu\mu$g./ml.)	Co-58 Vitamin B_{12} Injected (μg.)	Co-58 Vitamin B_{12} Retained (μg.)	Time in Days for Serum Vitamin B_{12} Level to Fall to 140 $\mu\mu$g./ml.	Time in Days for Serum Vitamin B_{12} Level to Fall to Pre-injection Level
1	(1) 127	50	36	35+	35+
	(2) 153	1,000	337	70	58
2	(1) 126	100	57	26	33
	(2) 123	1,000	330	46	60
3	(1) 147	100	51	40	39
	(2) 134	1,000	290	56+	56+
4	(1) 125	1,000	320	38	53
	(2) 109	100	58	35	49+
5	(1) 129	1,000	161	51	53
	(2) 113	100	53·7	42	35+
6	(1) 212	1,000	310	—	52
	(2) 199	100	60	—	40

TABLE II.—*Utilization of Co-58 Vitamin B_{12} Retained*

Case No.	After 50 or 100 μg. Injection: (*a*) Taking 140 $\mu\mu$g./ml. Serum Vitamin B_{12} as Base-line (μg./Day)	After 50 or 100 μg. Injection: (*b*) Taking Pre-injection Serum Vitamin B_{12} as Base-line (μg./Day)	After 1,000 μg. Injection: (*a*) Taking 140 $\mu\mu$g./ml. Serum Vitamin B_{12} as Base-line (μg./Day)	After 1,000 μg. Injection: (*b*) Taking Pre-injection Serum Vitamin B_{12} as Base-line (μg./Day)
1	<1·0	<1·0	4·8	5·8
2	2·0	1·7	7·1	5·5
3	1·2	1·2	5·0	5·0
4	1·6	1·1	8·6	6·0
5	1·2	1·5	3·0	3·0
6	—	1·5	—	5·9

Discussion

In every case the duration of effect of the 1,000 μg. injection in maintaining the serum vitamin B_{12} level above the pretreatment level, or above the lower limit of normal (140 $\mu\mu$g./ml.), was never greater than twice the effect obtained from 100 μg. or 50 μg. injection in spite of the fact that the amount of vitamin B_{12} retained in the body after the large injection was three to ten times greater than the amount retained after the small injection (Figs. 1–6; Table I). In other words, the effect of an injection of vitamin B_{12} in maintaining serum vitamin B_{12} levels above the pretreatment level or above the lower limit of normal is not proportional to the amount of vitamin B_{12} retained in the body after an injection.

There seems to be no doubt about the findings. So far as is possible the injections were given at the same serum vitamin B_{12} level in each patient, and the same pattern was seen whether the small injection was given before or after the large injection. The possibility that urinary excretion of the injected Co-58 vitamin B_{12} continued for more than 24 hours after injection was investigated in detail and was not found to be a significant factor. The intestinal excretion of injected Co-58 vitamin B_{12} in the doses used is trivial (unpublished observations) and can be disregarded as a relevant factor. It is known that Co-58 vitamin B_{12} may undergo deterioration *in vitro* (Lester Smith, 1959), and the possibility that this was a factor was also considered: the repetition of the pattern in every case studied was taken as evidence against this, and additional evidence was obtained when it was found that in two cases a

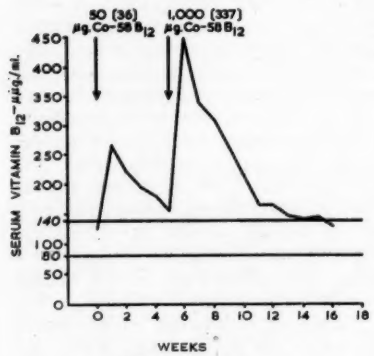

FIG. 1.—Case 1.

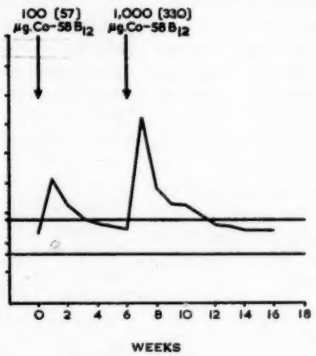

FIG. 2.—Case 2.

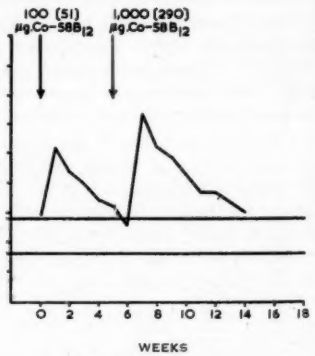

FIG. 3.—Case 3.

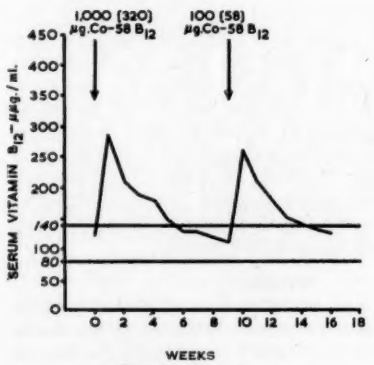

FIG. 4.—Case 4.

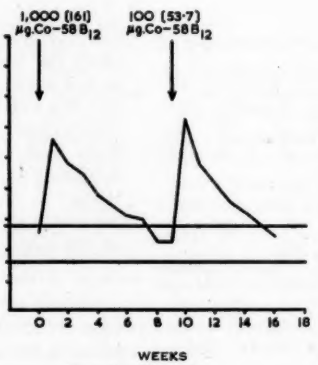

FIG. 5.—Case 5.

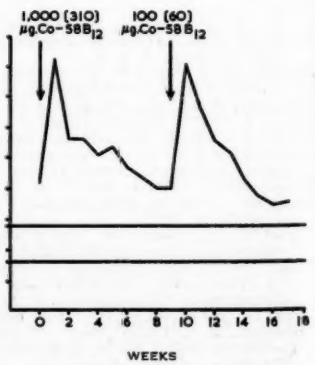

FIG. 6.—Case 6.

sample of the Co-58 vitamin B_{12} injected had not lost any of its microbiological activity between the time of use and the time the samples of sera were assayed.

The significance of the findings cannot be established with certainty in the light of our present knowledge of the metabolism of vitamin B_{12}. It has already been suggested that vitamin B_{12} does not exist as such in man but as an active derivative (Adams, 1961). The findings reported here raise the possibility that, at least with injection of large amounts of vitamin B_{12}, there may be a second metabolic pathway which involves conversion of the injected vitamin to an inactive form.

For practical purposes these patients with Addisonian pernicious anaemia do not absorb vitamin B_{12} from the intestine, and their intake of vitamin B_{12} is by injection; one might expect, therefore, that the utilization of injected vitamin B_{12} obtained from the formula used might represent the physiological requirement for vitamin B_{12} in man. It is scarcely likely that the physiological requirement varies with the amount of vitamin B_{12} injected, and one must conclude that the physiological requirement for vitamin B_{12} and the utilization of injected vitamin B_{12} as defined here are not necessarily the same, although this may be the case at certain lower dosage levels.

The aim of treatment of a patient with Addisonian pernicious anaemia is to achieve and maintain a serum vitamin B_{12} level within the normal range. It is obvious from the results that relatively little is to be gained by using an injection of 1,000 μg. in preference to an injection of 100 μg. The results reported here, and those obtained from a larger series of patients still under observation, tend to confirm the view that an injection of 100 μg. of vitamin B_{12} every three to five weeks is an economical and adequate maintenance treatment in most patients with pernicious anaemia.

Summary

A study of six patients with Addisonian pernicious anaemia has shown that large injections (1,000 μg.) of vitamin B_{12} do not have the expected effect in maintaining serum vitamin B_{12} levels above the lower limit of normal as compared with the effect of small (50 or 100 μg.) injections of vitamin B_{12}. This phenomenon is not due to the larger amount excreted after the 1,000 μg. injection, and it is possible that in the case of the larger injection at least some of the injected vitamin B_{12} may be inactivated in the body. From the results it appears that 100 μg. intramuscularly every three to five weeks is the most economical and effective form of maintenance therapy in patients with pernicious anaemia.

I am grateful to Dr. J. A. W. McCluskie for his advice and criticism and to Professor E. J. Wayne for facilities in his department.

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The Nuffield Provincial Hospitals Trust has made a grant of £3,500 over the next three years to enable the Bristol Industrial Therapy Organization to start a workshop for psychiatric patients who are well enough to leave hospital but not able to compete in open employment.

Preliminary Communications

Simultaneous Intramuscular Injection of Oxytocin and Ergometrine: A Tocographic Study

Responsible obstetric opinion in regard to the management of the third stage of labour and the treatment of post-partum haemorrhage has undergone some modification in recent years. Ergometrine, for long the sheet anchor of treatment in post-partum haemorrhage, is no longer condemned before delivery of the placenta, but is injected at the first sign of bleeding. Moreover, in many hospitals throughout this country nowadays, ergometrine is given routinely, intramuscularly or intravenously, as soon as the head is delivered. Those who practise the method emphatically believe that its use brings a rewarding reduction in the incidence of post-partum haemorrhage and in the size of the haemorrhage when it occurs—and that imprisonment of the placenta occasionally is a small price to pay for this reward.

Oxytocin—which might be regarded as more physiological—has not been generally favoured in this connexion, chiefly because, in the past, profound shock has occasionally followed its use. But there is little doubt that many of the mishaps of former years occurred with the old "pituitrin," and some were the result of misuse of the drug, sometimes amounting to irresponsibility, with too large and often-repeated dosage. Moreover, it must be remembered that the pure preparations of oxytocin now available are probably safer than those formerly used. In the United States of America oxytocin is employed a good deal in the conduct of the third stage of labour.

Case No.	Day of Puerperium	Details of Injection and Dose	Time of Onset of Oxytocic Response
		Main Series	
1	7	Oxytocin 2·5 u. Ergometrine 0·25 mg.	3′ 40″
2	6	,, ,,	3′ 30″
3	3	,, ,,	2′ 30″
4	6	,, ,,	2′ 0″
5	6	,, ,,	1′ 50″
6	2	,, ,,	1′ 20″
7	3	,, ,,	1′ 30″
8	2	,, ,,	2′ 30″
9	2	,, ,,	3′ 10″
10	2	,, ,,	2′ 40″
11	3	,, ,,	3′ 0″
12	2	,, ,,	3′ 40″
13	3	Oxytocin 5 u. Ergometrine 0·5 mg.	3′ 30″
14	3	,, ,,	2′ 10″
15	7	,, ,,	2′ 0″
16	3	,, ,,	2′ 20″
17	9	,, ,,	4′ 30″
18	7	,, ,,	1′ 20″
		Control Series	
19	3	Oxytocin 5 u.	2′ 40″
20	3	,,	4′ 0″
21	2	,,	3′ 10″
22	3	,,	2′ 20″
23	2	,,	2′ 0″
24	2	,,	3′ 0″
25	3	,,	2′ 10″
26	3	,,	4′ 0″
27	3	,,	1′ 30″
28	2	,,	1′ 10″
29	6	Oxytocin 2·5 u.	2′ 30″
30	3	,,	2′ 0″

Mean of main series = 2 min. 37 sec. (S.D. 55 sec.)
,, ,, control ,, = 2 ,, 32 ,, (,, 53 ,,)

It is pertinent, in view of these trends, to examine carefully the action of these drugs on the parturient uterus and, in particular, how quickly they exert their effect.

This short communication reports a recent study of a new oxytocic preparation, "syntometrine," which combines oxytocin and ergometrine in a single ampoule and is claimed to have the merits of both drugs.* It was undertaken as a sequel to earlier investigations which studied the speed of action of ergometrine (Embrey and Garrett, 1958) and oxytocin (Embrey, 1959) alone.

METHOD

Records of uterine contractility were obtained in the lying-in period from 18 patients, either externally or internally, using the Oxford tocograph (Embrey, 1958). After a control period to record the spontaneous uterine activity, an intramuscular injection of syntometrine was given, and the effect on uterine contractility recorded graphically. In each case the time of onset of the oxytocic response was accurately measured for comparison with the control series. The Table shows dosage and relevant details.

RESULTS

In every case a typical oxytocic response was recorded. Examples of the records obtained are shown in Figs. 1 and 2. The mean latent period from the moment of injection to the onset of the oxytocic effect was 2 minutes 37 seconds. In a control series of 12 cases the mean speed of action of intramuscular oxytocin alone was 2 minutes 32 seconds. In the series previously reported the corresponding action times for ergometrine were: intravenous ergometrine, 41 seconds; intramuscular ergometrine with hyaluronidase, 4 minutes 47 seconds; and plain intramuscular ergometrine, 7 minutes.

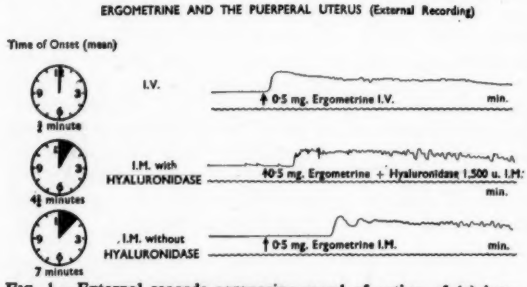

FIG. 1.—External records comparing speed of action of (*a*) intravenous ergometrine, (*b*) intramuscular ergometrine with hyaluronidase, (*c*) plain intramuscular ergometrine.

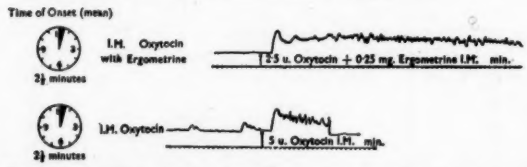

FIG. 2.—External records comparing speed of action of (*a*) intramuscular oxytocin with ergometrine, and (*b*) intramuscular oxytocin. Note waning effect at 15 min. when tocograph slipped.

COMMENT

The earlier studies showed that the addition of hyaluronidase to the injection quickens the speed of action of intramuscular ergometrine by approximately 2 minutes, reducing the latent period from 7 to about 5 minutes. Intravenous ergometrine, however, has five times this speed of action, being effective in less than one minute. Clearly, intravenous ergometrine has no peer and must remain the method of choice in dealing with sudden post-partum haemorrhage. On the other hand, for the midwife who normally is not trained to make an intravenous injection the ergometrine–hyaluronidase mixture provides a substitute to intravenous therapy, which is extensively used and has been strongly recommended (Kimbell, 1954).

The present study confirms that, given intramuscularly, oxytocin acts much more quickly than ergometrine and is effective in approximately 2½ minutes. Moreover, intramuscular oxytocin is much quicker in action than the ergometrine–hyaluronidase mixture—in fact, almost twice as fast. From the point of view of speed it is the best substitute for intravenous ergometrine.

The action of the two drugs is different in one important respect, however, and here ergometrine has the advantage. After the injection of ergometrine there is a well-marked uterine spasm, commonly lasting 45 minutes or more (on which, of course, its renowned haemostatic property depends), while the oxytocic effect may be evident three hours after the injection. It has commonly been said in the past that oxytocin, unlike ergometrine, does not produce tetanic contraction of the uterine muscle. This is not true. The difference in effect between the two drugs is merely a matter of degree. The larger doses of oxytocin produce quite well marked, though comparatively short-lived (about 15–20 minutes) spasm, with a total effect averaging 30 minutes. None the less, it has to be admitted that the spasm-producing properties of oxytocin are not nearly so striking as those of ergometrine. Syntometrine, therefore, may prove a useful tool in clinical practice, for it would seem profitable, in circumstances where an intravenous injection cannot be given, to combine intramuscular oxytocin, for its speed of action, with intramuscular ergometrine.

SUMMARY

A combined intramuscular injection of oxytocin and ergometrine has been studied tocographically. With the strength and duration of action of ergometrine the preparation has the speed of oxytocin and is effective in 2½ minutes.

ADDENDUM.—A clinical trial of the new preparation syntometrine is in progress. Experience in the first 46 cases has been encouraging. In 44 cases the injection was given before the end of the second stage of labour. In these there was no case of post-partum haemorrhage, and the loss was less than 10 oz. (280 g.) in all but two cases. No difficulty was experienced in expressing the placenta, and the third stage of labour was completed within five minutes in 33 cases and in the remainder within ten minutes.

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*The ampoules used in this study, supplied by Sandoz Products Ltd., through the courtesy of Dr. H. Holgate, contained oxytocin 5 units and ergometrine 0.5 mg.

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Medical Memoranda

Acute Hydramnios, with Twins, Successfully Treated by Abdominal Paracentesis

Rivett (1933), Lloyd (1943), Erskine (1944), Danziger (1948), Hammond (1952), and Brown (1958) have reported cases in which amniotomy by abdominal paracentesis has allowed a plural pregnancy, complicated by acute hydramnios in the middle trimester, to continue until the delivery of a normal living child.

In the following case *two* normal living children were secured. We have searched the literature and have not found a single report of a similar case.

CASE REPORT

The patient, aged 39, presented on August 11, 1960, complaining of abdominal swelling for two weeks. She had been married for seven years and had had no previous pregnancy. What she regarded as her last normal period began on May 16. At the beginning of August she became aware of an abdominal swelling which had increased rapidly in size. Abdominal examination revealed a tense cystic swelling of the size of a normal 36-weeks pregnancy. Vaginal examination confirmed that the swelling was uterine in origin. *X*-ray examination showed two foetuses of just over 16 weeks' maturity.

On admission to hospital on August 17 the patient was slightly orthopnoeic. The abdominal swelling had increased to the size of a normal full-time pregnancy. Foetal parts could not be palpated and foetal heart sounds could not be heard. The abdominal circumference was 39 in. (99 cm.). She became more orthopnoeic and the abdominal swelling continued to increase rapidly. On August 22 amniotomy was performed by abdominal paracentesis, using a lumbar-puncture needle. After 3 pints (1.7 litres) of liquor amnii had been withdrawn the needle blocked and the operation was discontinued. Within 24 hours a further 6 pints (3.4 litres) of liquor amnii was drained by a second amniotomy, this time using a 2.5-mm.-bore trocar and cannula. The next day the patient felt more comfortable and the uterus was the size of a normal 26-weeks pregnancy. The patient was allowed home on September 3, by which time foetal heart sounds could be heard.

When she was seen at the antenatal clinic on September 12 she had felt movements for one week. On October 3 the uterus was the size of a normal 28-weeks pregnancy, and an *x*-ray film showed normal twins of just under 24 weeks' maturity. By October 24 the size of the uterus had increased to that of a normal 36-weeks pregnancy. Her blood-pressure had remained normal and the urine clear.

One week later she was readmitted to hospital because of increasing dyspnoea and abdominal discomfort. On November 9 paracentesis was repeated, using the trocar and cannula. Six pints (3.4 litres) of liquor amnii was drained. This reduced the abdominal circumference from 41½ to 37½ in. (105 to 95 cm.). Five days later 5 pints (2.8 litres) of liquor amnii was removed, making a total of 20 pints (11.4 litres).

On November 19 the membranes ruptured and several pints of liquor amnii drained through the vagina. Labour began 18 hours later. The first twin was presenting by the vertex. The second stage was reached in 21½ hours, but its completion was delayed by uterine inertia. Pudendal nerve block was achieved, and after episiotomy the first twin was easily delivered with forceps. The child, a girl, cried soon after birth and weighed 3 lb. 11 oz. (1,670 g.).

Soon after the delivery of the first twin the frank breech of the second entered the pelvis. Very little liquor amnii escaped from the second sac when the membranes over the breech were torn. The delivery was completed by the Burns Marshall method. The second child, another girl, was born seven minutes after the first, cried soon after birth, and weighed 3 lb. (1,360 g.).

The complete uniovular placenta was expelled without difficulty three minutes later and showed no abnormality. Ergometrine was then given and the perineum was repaired. Blood loss was 6 oz. (170 ml.).

The puerperium was uncomplicated. Lactation was suppressed. The patient's haemoglobin was 80% (Sahli) on the third puerperal day and she was allowed home on the eighth day.

The twins were nursed in the paediatric department until almost 5 lb. (2,270 g.) in weight. They continued to make good progress at home.

COMMENT

The estimates of foetal maturity made from two *x*-ray examinations, the one eight weeks after the other, were in agreement, the maturity on August 11 being estimated at just over 16 weeks and on October 3 at just under 24 weeks. This means that the last true menstrual period probably began on April 18, four weeks before what the patient thought to be her last normal period.

It follows that the first and second amniotomies were performed towards the end of the eighteenth week. The fact that 9 pints (6.1 litres) of liquor amnii was removed within 24 hours at this time is evidence of the severity of the hydramnios. Amniotomy was repeated at 29 weeks and near the end of the thirtieth week, and the patient was delivered about the end of the thirty-first week.

We thank Professor David Fyfe Anderson for permission to report this case.

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The objects of the Mobile Physiotherapy Service Association, the president of which is Sir Cecil Wakeley, are to promote the establishment of mobile physiotherapy services where they are needed, and to advise and co-ordinate services already established. These services take massage, electrical, and exercise therapy to the homes of those who are (*a*) physically incapable of attending a hospital department where treatment is free under the National Health Act, and (*b*) unable to afford the full cost of home treatment. Chartered physiotherapists drive their own vans equipped with portable apparatus for use in the patients' homes. This service is dependent upon voluntary help. The secretary's address is Mrs. J. HINE, Walled Cottage, Kinnersley, Sidlow, near Reigate, Surrey.

Reviews

ABDOMINAL CRISES

Intra-abdominal Crises. By Kenneth D. Keele, M.D., F.R.C.P., and Norman M. Matheson, F.R.C.S., M.R.C.P., F.A.C.S. (Pp. 397+xii; illustrated. 50s.) London: Butterworths. 1961.

Every surgeon examining a patient with an acute abdominal crisis applies unconsciously a whole lifetime of experience. In taking the history he sieves important items of information from a host of irrelevances. Almost without realizing it, he is aware of the patient's general condition, his flushed or sallow complexion, his eyes bright or dull, his restlessness or apathy. All these impressions, along with the more precise findings of the physical examination, he receives and registers and judges in the light of his knowledge of disease and the half-forgotten memories of previous cases.

The difficulty lies in putting all these things into words for the benefit of younger and less expert readers, and few authors have succeeded in clothing the bare bones of textbook information with living flesh. The authors of the present volume have attempted to do so, and they have the advantage that as a physician-surgeon team they are equally competent to deal with the conditions commonly dubbed surgical and those for which no operation is indicated. On the whole they have made a good job of it, though in places they have made the mistake of trying to include too much, so that such subjects as the islet-cell tumour of the pancreas, surely very rare as a cause of an acute abdominal crisis, vie with the much more important acute pancreatitis.

Perhaps the best chapters in the book are those given to the non-surgical diseases, the metabolic causes of acute symptoms, the hepatic and biliary and renal crises, the gastroenteritis and poisoning, and colitis. There is a useful appendix which describes in simple terms the many laboratory investigations which may be needed, indicating their range of usefulness and the significance of their findings.

C. F. W. ILLINGWORTH.

GUIDE TO NEUROLOGY

Clinical Neurology. By Sir Russell Brain, Bt., D.M., F.R.C.P.(Lond.). (Pp 399+viii; illustrated. 38s.) London, New York, Toronto: Oxford University Press. 1960.

Sir Russell Brain's *Textbook of Neurology* is a well-known work of reference which is much valued by general physicians and neurologists. In this new publication he has undertaken a difficult task, for he has attempted to present to the general practitioner or senior student all that he needs to know of neurology. It might be argued that what the general practitioner really wants to know about is the differential diagnosis of symptoms, such as pain in the face, syncope, difficulty in walking, blurring of vision, vertigo, acute confusion, coma, etc. This book provides the answer to some of these problems very competently (e.g., in the case of epilepsy, headache, and coma), but for others the reader may have difficulty in finding the advice he requires.

It is, of course, easy to find something to criticize in a book of this kind, for many of the obvious omissions may be deliberate. One feature which strikes the reviewer is an absence of any feeling of therapeutic urgency when quick action is a matter of life and death. Thus a severe case of acute infective polyneuritis requires prompt transfer to a centre for artificial respiration. Or again, status epilepticus will be fatal if the convulsions are not stopped quickly, and for this a single injection of paraldehyde, as advised on p. 142, may be quite inadequate. It will surprise many to read that the value of parenteral vitamin B_1 in alcoholic polyneuritis or Korsakoff's psychosis "is disputed," for most think that parenteral vitamin B_1 preparations should always be given as a matter of urgency in the obscure confusional states and in polyneuropathies of the non-acute type.

However, though the therapeutic urge in this book is at times half-hearted, it has great merit as an elementary guide to diagnosis.

W. RITCHIE RUSSELL.

SCHWANN'S LETTERS

Lettres de Théodore Schwann. Edited by Marcel Florkin. (Pp. 274; illustrated. Fr. 250.) Liège: Société Royal des Sciences de Liège, Université de Liège. 1961.

In 1839, at the age of 29, Théodore Schwann wrote a small book *Mikroskopische Untersuchungen über die Uebereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen*, which was the foundation of the cellular theory. In the ten years before this he had undertaken a series of researches of the most productive and original type. After 1839 until his death he made no further major contribution to scientific literature.

Marcel Florkin's collection of Schwann letters covers the years after 1839. In that year he was appointed professor at Louvain, and in 1848 moved to Liège, where he remained for the rest of his academic life. Many of the letters are illustrative of a continuous correspondence between Schwann and his colleague, the professor of zoology, P. K. Van Beneden, and throw an interesting light on the life and activities within the Belgian universities in this period. A further set of letters refers to the curious relationship that Schwann had with the investigation of the supposed stigmata of Louise Lateau, and the final series of letters in this collection covers the time of the international gathering in honour of the fortieth anniversary of the publication of his great work.

It was a great period in the development of the medical and biological sciences in Europe, and throughout the correspondence names which are still familiar to us, such as Johannes Müller, who was Schwann's teacher in Berlin, Henle, who was a fellow-pupil, the great surgeons such as Winiwarter, who held the chair of surgery at Liège, Du Bois-Reymond, the founder of electro-physiology, and many others, recur continually.

For all those interested in this remarkable man and in the times in which he lived these letters form a fascinating and carefully annotated volume. One is grateful to the editor for the continuity that is produced by his short biographies and by his brief descriptions of the circumstances under which each letter was written.

G. CAUSEY.

PARASITOLOGY IN EUROPE

Parasitologie für Ärzte. By Otto Jírovec, assisted by Dr. J. Jíra, Dr. E. Kmety, Dr. J. Kramář, Dr. M. Petrů, and Dr. B. Rosický. (Pp. 684+xi; illustrated. DM. 93.65.) Jena: Veb Gustav Fischer Verlag. 1960.

There are a number of good books on medical parasitology, the majority of which are oriented towards tropical medicine. This is probably the first book to be written from the standpoint of workers in Europe, whose requirements on the subject are much more

limited, and yet who need special knowledge on certain branches of parasitology. It is here that Professor Jírovec's experience is of unique value, and his own researches on these parasites and the diseases they cause have done much to advance our understanding of them. It is fortunate also that the author has had the advantage of the collaboration of specialist workers, such as Dr. J. Jíra; this adds to the value of the publication.

The book is written very much from the practical angle, and contains both in the preliminary chapters and in two appendices useful descriptions of techniques. The main part is divided into sections on protozoa, helminths, and arthropods, and a clear account of each parasite is given under the following headings—morphology and life cycle, clinical features, laboratory diagnosis, therapy, epidemiology, and control. Although the book concentrates on European parasites, the tropical forms are mentioned, because cosmopolitan travel is apt to introduce exotic species to our continent; but instead of malaria, for instance, occupying a large chapter, it is described in 34 pages, while toxoplasmosis, on the other hand, is given almost the same amount of text. The book is specially valuable for its description of the latter condition and of infection by *Trichomonas vaginalis* and *Pneumocystis*, on all of which subjects the author is an authority.

The book is beautifully illustrated by 285 pictures, diagrams, and distribution maps; includes a number of coloured photographs; and contains 27 tables of epidemiological or diagnostic characters. It possesses a good index, and an interesting bibliography of Czechoslovakian works on parasitology as well as the usual monographs and textbooks.

P. C. C. GARNHAM.

DELINQUENT AND NEUROTIC CHILDREN

Delinquent and Neurotic Children. A Comparative Study. By Ivy Bennett, M.A., Ph.D. (Pp. 532+xii. 45s.) London: Tavistock Publications. 1960.

Using material derived from children under treatment in a rural English Child Guidance Service, Dr. Bennett presents the case histories of 100 boys and girls—50 delinquent and 50 neurotic, matched for age and intelligence. Her primary aim is to compare the divergent routes taken in emotional development by these groups of children from their earliest years. The approach is psycho-analytic.

Delinquent children tended to come from "unstable" homes, in contrast to the "stable" homes of neurotic children; there was no difference in the social level from which delinquent and neurotic children were derived. Chronic physical illness was common among the parents of both delinquent and neurotic children, and both groups of children themselves gave frequent histories of having suffered from chronic disease. Delinquents often had parents who showed antisocial tendencies, while neurotics were apt to have neurotic parents. Both delinquent and neurotic children tended to have disturbed relationships with their siblings. Delinquent children were found to have experienced more frequent interruption of the mother–child relationship in early years; separation of the child from its home and parents, or absences of the parents, occurred more frequently in delinquents than in neurotics. Delinquent children "had been breast-fed less often than the neurotics, and when breast-feeding did occur, they were weaned much earlier than the neurotics." A marked failure was found in the sphere of social relationships among both delinquent and neurotic groups. Delinquent children were frequently disobedient and aggressively defiant; whereas neurotic children were often "over-good." The delinquent children in the survey usually came from larger families than did the neurotics. As the author appreciates, the value of this research would have been greatly increased had she been able to include comparable material from a group of normal children.

T. FERGUSON.

MEDICAL CARICATURES

Medizinische Karikaturen von 1800 bis zur Gegenwart. Compiled and introduced by Helmut Vogt. (Pp. 184; illustrated. No price.) Munich: J. F. Lehmann Verlag. 1961.

Vogt's *Medical Caricatures from 1800 to the Present Day* reproduces 315 cartoons from German, French, British, and American sources in that numerical order. A textual introduction traces the movements in medicine—from smallpox vaccination through homoeopathy to bacteriology, roentgenology, and rejuvenating hormones—which have attracted the humorous artist, and the remaining cartoons are also classified by subject. The author's favourite sources seem to be *Simplicissimus* and *Le Fou Rire*, which provide much of the most cynical and bawdy material, and he has an evident liking for the macabre in Hogarth or Daumier. Examples of merely rather coarse wit, both German, are a picture entitled "Nursing Infant Hygiene Overdone," showing a woman immersing her breast in a saucepan of apparently boiling water, and one of a young woman presenting a plump elevated backside to a snake charmer, whose music is expected to bring forth the tapeworm for which she has declined to take a vermifuge. French and English cartoons have their captions in both the original and in German: the slang of some of those in German only may defeat all but those with exceptional linguistic ability. This collection has some historical interest, but it is thoroughly sordid in comparison with *Mr. Punch among the Doctors* (Methuen, 1933), from which it borrows only three items, and those among the least complimentary to the profession.

L. P. GARROD.

BODY FLUIDS IN PREGNANCY

Fluid Balance in Obstetrics. A Critical Review. By Philip Rhodes, M.A., M.B., F.R.C.S.(Eng.), M.R.C.O.G. (Pp. 169+x. 25s.) London: Lloyd-Luke (Medical Books) Ltd. 1960.

In this book an attempt has been made to summarize the problems arising from changes in the volume and composition of the body fluids in pregnant women. The author writes as a clinician for other clinicians, and has not been responsible for any research in this field; he is, however, trying to close the gap between the laboratory and the wards and to provide a working basis for obstetric practice. There is much free quotation from various sources of information on and discussions of important aspects of body composition. It seems a pity, however, that the author has been content so often to quote from textbooks rather than first hand from the original papers.

Some of the recommendations for replacement or maintenance of water, potassium, and sodium are generous if not lavish, and appear to be based on analogy with orthodox general surgical practice. There is now some evidence that such large provisions of water and salts are not always justified and sometimes undesirable. In providing obstetricians and others who are interested in the physiology of pregnancy and

parturition with a good many facts, Dr. Rhodes has also made plain the wide gaps in our knowledge; perhaps with this stimulus others will now set about remedying them. The time has now come when obstetricians should measure accurately the daily intake and output of normal women before and after delivery of their babies, and so avoid speculative estimates of the daily requirements of water and minerals both for those whose pregnancy is normal and for those with complications, such as eclampsia and caesarean section.

A. W. WILKINSON.

CHEMISTRY OF THYROID DISEASES

The Chemistry of Thyroid Diseases. By Rosalind Pitt-Rivers, M.Sc., Ph.D.London, F.R.S., and Jamshed R. Tata, M.Sc. (Pp. 83+xii. 36s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

This short account is written by two workers who have themselves contributed substantially to our understanding of the functions of the thyroid hormones both in health and in disease. In itself it does not provide a background of basic knowledge sufficient to understand fully the significance of the results which they describe, and it should be read in conjunction with the larger work on *The Thyroid Hormones* by the same authors. Quantitative and qualitative abnormalities of iodine metabolism in both hypothyroidism and hyperthyroidism are well summarized, and there is a full account of the abnormal serum iodoproteins—compound X and S-1 iodoprotein—which may be found in cases of cancer of the thyroid. An account of the immunological aspects of thyroid disorders occupies only 12 pages of text, but it is clear and places the subject in correct perspective.

Those who are already interested in thyroid disease and aware of the trend of current research will find much to interest them, and moreover will be pleased to have many up-to-date references. Some preliminary reading would be necessary before the general reader could obtain full advantage from this stimulating book, but the effort would be rewarding.

E. J. WAYNE.

VISUAL SYSTEM AND BRAIN INJURY

Visual Field Defects after Penetrating Missile Wounds of the Brain. By Hans-Lukas Teuber, William S. Battersby, and Morris B. Bender. (Pp. 143+xi; illustrated. 38s.) London: Oxford University Press. 1960.

This is a fascinating and important monograph which represents the conclusions derived from the intensive study of the defects in the visual fields produced by cerebral gunshot injuries sustained in the last war and the Korean campaign; some of these were studied soon after injury, but the main group (46) came under observation more than five years after injury and were intensively observed over periods varying from several months to eight years. Routine perimetry and campimetry were supplemented by other methods of exploration of the visual function: flicker perimetry, colour perimetry, and the exploration of such retinal and perceptual processes as dark adaptation, depth perception, tachistoscopic appreciation, the recognition of hidden figures, and the appreciation of real and apparent motion.

Much of our knowledge of the central organization of the visual pathways is derived from such studies carried out by observers during and after the first world war in Great Britain, France, and Germany, among whom the British names of Gordon Holmes, William Lister, and George Riddoch are particularly prominent. The observations of these pioneers have not been refuted but merely supplemented in details by similar studies during and after the second world war. Nowhere else, however, has so large a series of such cases been studied so extensively. Some important conclusions emerge. Contrary to the classical view the claim is made that the macular fibres cannot form a distinct bundle running between the fibres mediating the upper and lower peripheral quadrants of the visual field which occupy the ventral and dorsal aspects of the optic radiations. The general lack of congruence in homonymous field defects regardless of the localization of the wound suggests to the authors that the current conception that the visual system is accurately projected topographically is wrong, even at the level of the striate cortex. They found that after a circumscribed lesion various aspects of visual performance are widely affected, sometimes subtly, sometimes grossly, often over the entire field across the midline, remote effects which suggest that the functional activity of all parts depend on the integrity of every part. The evidence brought forward to support these and other suggestions is certainly weighty, and will have to be carefully studied both by neurologists and ophthalmologists as well as anatomists and physiologists interested in the higher organization of the visual system.

STEWART DUKE-ELDER.

DAMAGES FOR PERSONAL INJURY

Medical Evidence in Personal Injury Cases. The Medico-Legal Aspects of an Action for Damages Arising out of a Personal Injury. By Dorothy Knight Dix and Alan H. Todd, M.S., B.Sc.London, F.R.C.S.Eng. (Pp. 242+xii; illustrated. 42s.) London: H. K. Lewis and Co., Ltd. 1961.

The title exactly defines the subject-matter of this book, which is limited to an important and specialized part of the medico-legal work about which a doctor may require information.

The authors, a barrister and a surgeon, are both experienced and have practical knowledge of the courts, so that they know the requirements of the doctor. These extend somewhat beyond those of undergraduates preparing for examinations, and the information the book gives is very relevant to the consultant and practitioner who has the responsibility of making reports and giving evidence in connexion with personal injury. There is ample information on the scope of medical evidence and on the examination and writing of a medical report. The examples given are useful, particularly as those who write medical reports need to appreciate the meaning of an agreed report. Several chapters cover the medico-legal aspect of clinical conditions, such as fractures and joint injuries, and these are of more value to the lawyer than the doctor, who must look elsewhere for details of the union of bone and treatment of injuries of the locomotor system. Injuries of the central nervous system are described, so that the reader can appreciate the medico-legal aspect of psychoneurosis, changes of personality, and comparable conditions. These are as fascinating a study as the advice given to the doctor who is faced with writing a report or giving evidence when he thinks the patient suffers from hysteria or suspects that he is a malingerer. Many aspects of giving evidence are described, and legal cases are quoted and listed. There are glossaries of legal and medical terms. This book should be known to the medical profession, as the guidance it gives is helpful and authoritative.

ST. J. D. BUXTON.

MASSACHUSETTS C.P.C.s

Clinicopathological Conferences of the Massachusetts General Hospital. Selected Medical Cases. By Benjamin Castleman, M.D., and H. Robert Dudley, jun., M.D. (Pp. 295+xiv; illustrated. 90s.) London: J. and A. Churchill, Ltd. 1960.

The clinicopathological conference—now universally contracted to C.P.C.—has become an important part of the educative programme of most teaching hospitals. Whether the student is an undergraduate or a post-graduate, it calls for his active participation, and by bringing together anatomy, physiology, biochemistry, pathology, and therapeutics provides an intellectual stimulus which, thank goodness, has come to replace the boredom of long hours of unsupplemented didactic lectures.

The Massachusetts General Hospital is the birthplace of the C.P.C. The idea originated at the turn of the century in the mind of a young Harvard medical student, W. B. Cannon, who later became a distinguished professor of physiology, but the conferences were initiated and conducted for many years by Dr. Richard Cabot and Dr. Tracy Mallory. Each week for many years a conference has been reported in the *New England Journal of Medicine*, and many must be the houseman and registrar in England who, with the Membership in view, has followed the proceedings and faithfully not looked at the anatomical findings until he has made his own diagnosis. Such has been the popularity of these conferences that they have been syndicated to other medical schools and translated each week into Japanese and Spanish. The pattern of the C.P.C.s at the Post-graduate Medical School in London, which are reported in this *Journal* monthly, follows closely the pattern set in Boston.

The present volume is a selection of some 50 medical C.P.C.s held at the Massachusetts General Hospital—some held as long ago as 1936 but most of post-war vintage. A wide range of subjects is covered, and where appropriate an addendum mentions the contribution that recent advances would have made to the diagnosis or understanding of the case. Nobody interested in medicine, whether student, houseman, specialist, or general practitioner, could fail to derive pleasure and intellectual improvement from browsing through this book.

R. I. S. BAYLISS.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Clinical Disturbances of Renal Function. By Abraham G. White, M.D., F.A.C.P. (Pp. 468+x; illustrated. 73s. 6d.) Philadelphia, London: W. B. Saunders Company. 1961.

Growing Old. Problems of Old Age in the Australian Community. Edited by Alan Stoller. (Pp. 205+ix. 15s.) Melbourne: F. W. Cheshire, for the Victorian Council for Mental Hygiene. 1961.

Synthetic Ion-Exchangers. Recent Developments in Theory and Application. By G. H. Osborn, F.R.I.C. Second edition. (Pp. 346+x. 50s.) London: Chapman and Hall Ltd. 1961.

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THE KIDNEY AND ERYTHROPOIESIS

More than sixty cases of primary disease of the kidney in conjunction with increased red-cell count have now been reported. Carcinoma has been the commonest renal lesion, while 3 to 4% of patients with renal carcinoma have abnormally high red-cell counts. In a recent survey of 135 consecutive cases of hypernephroma, for example, J. S. Hewlett and his associates[1] found four with erythrocytosis. Many of the reported cases are summarized in the papers of A. Damon and his collaborators,[2] J. H. Lawrence and W. G. Donald,[3] and H. F. Barnard.[4] It is noteworthy that the haematological findings, though often described as polycythaemic, do not include the leucocytosis, thrombocytosis, and splenomegaly usual in polycythaemia vera, and the level of the alkaline phosphatase of the leucocytes, when it has been assessed, has proved to be normal,[5 6] whereas it is almost invariably high in polycythaemia vera. "Erythrocytosis" or "erythrocythaemia" would therefore seem more appropriate than "polycythaemia" as descriptive terms for the blood picture in these cases. Similar blood changes have been noted in patients with benign tumour[7] or with non-neoplastic renal lesions such as hydronephrosis or polycystic disease.[8]

The accumulation of case reports illustrating the association between renal and erythrocytic disorders suggests that there may be a causative link between them, but much stronger evidence in favour of this supposition is provided by the fact that surgical removal of the tumour or affected kidney has generally been followed by correction of the erythrocytosis. J. Forsell[9] as long ago as 1946 suggested that renal tumours might be capable of inducing excessive erythropoiesis, and the results of nephrectomy lend support to this view. This hypothesis, and the corollary that the erythropoietic effect might be mediated by a humoral mechanism,[10] were initially derived from clinical observations, but studies on experimental animals have also shown that the kidney may be an important source of plasma factors controlling the production of red cells.

Erythropoietic factors in the plasma have been much studied recently,[11–13] and various methods have been developed for bioassay of them. The multiplicity of techniques and the complicated nature of some of them make exact comparisons of results from different laboratories difficult and certainly account for some of the contradictory findings reported, but there seems little doubt that two major factors exist which can stimulate erythropoiesis. The first of these is a non-dialysable mucoprotein commonly called "erythropoietin."[14] This factor is probably the chief physiological regulator of erythropoiesis, acting at a very early stage in the chain of red-cell production by stimulating the haemocytoblast or proerythroblast to differentiate.[15] The production of erythropoietin appears to be a function of the kidney,[16 17] and, despite differing experimental results and alternative interpretations,[18–20] to depend on renal integrity. The second chief factor with stimulatory activity is not a protein,[21] is soluble in ether, and is found in the plasma of patients with primary and secondary polycythaemia. Whether this factor is a cause of these diseases or is a by-product of marrow hyperplasia is disputed.[22] It has not been shown to be produced by the kidney, and it is a less physiological stimulator than the mucoprotein erythropoietin, since it causes an erythrocytosis of microcytic cells without an increase in haemoglobin.[23] With the proviso that there is no unanimity of opinion among workers in this perplexing field, it seems reasonable to conclude at present that the ether-soluble factor is probably not of primary importance in the genesis of renal erythrocytosis.

Clinical observations and laboratory experiment meet on common ground in some recent work. Hewlett and his co-workers[1] found that extracts

[1] Hewlett, J. S., Hoffman, G. C., Senhauser, D. A., and Battle, J. D., *New Engl. J. Med.*, 1960, **262**, 1058.
[2] Damon, A., Holub, D. A., Melicow, M. M., and Uson, A. C., *Amer. J. Med.*, 1958, **25**, 182.
[3] Lawrence, J. H., and Donald, W. G., *Ann. Intern. Med.*, 1959, **50**, 959.
[4] Barnard, H. F., *Brit. med. J.*, 1961, **1**, 1214.
[5] Mitus, W. J., Mednicoff, I. B., and Dameshek, W., *New Engl. J. Med.*, 1959, **260**, 1131.
[6] Rosenbach, L. M., and Xefteris, E. D., *J. Amer. med. Ass.*, 1961, **176**, 136.
[7] De Marsh, Q. B., and Warmington, W. J., *North. Med. (Seattle)*, 1955, **54**, 976.
[8] Jones, N. F., Payne, R. W., Hyde, R. D., and Price, T. M. L., *Lancet*, 1960, **1**, 299.
[9] Forsell, J., *Nordw. Med. (Seattle)*, 1946, **30**, 1415.
[10] Conley, C. L., Kowal, J., and D'Antonio, J., *Bull. Johns Hopk. Hosp.*, 1957, **101**, 63.
[11] Linman, J. W., and Bethell, F. H., *Factors Controlling Erythropoiesis*, 1960, C. C. Thomas, Illinois.
[12] Erslev, A. J., *Ann. Rev. Med.*, 1960, p. 315.
[13] Brecher, G., and Stohlman, F., Jr., in *Progress in Hematology*, Vol. II, edited by L. M. Tocantins, 1959, p. 110.
[14] Jacobson, L. O., Goldwasser, E., and Gurney, C. W., in *The Kinetics of Cellular Proliferation*, edited by F. Stohlman, 1959, p. 344.
[15] Erslev, A. J., *Blood*, 1959, **14**, 386.
[16] Jacobson, L. O., Goldwasser, E., Fried, W., and Plzak, L., *Nature (Lond.)*, 1957, **179**, 633.
[17] Naets, J. P., ibid., 1958, **181**, 1134.
[18] Mirand, E. A., and Prentice, T. C., *Proc. Soc. exp. Biol. Med.*, 1957, **96**, 49.
[19] Erslev, A. J., *Arch. Int. Med.*, 1958, **101**, 407.
[20] Osnes, S., *Brit. med. J.*, 1959, **2**, 650.
[21] Linman, J. W., Bethell, F. H., and Long, M. J., *J. Lab. clin. Med.*, 1958, **51**, 8.
[22] Penington, D. G., *Lancet*, 1960, **1**, 975.
[23] Linman, J. W., and Long, M. J., *Blood*, 1958, **13**, 226.
[24] Erslev, A. J., *Clin. Res. Proc.*, 1957, **5**, 141.
[25] Gurney, C. W., Goldwasser, E., and Pan, C., *J. Lab. clin. Med.*, 1953, **50**, 534.
[26] Gallagher, N. I., McCarthy, J. M., Hart, K. T., and Lange, R. D., *Blood*, 1959, **14**, 662.

prepared from a hypernephroma associated with erythrocytosis contained more erythropoietin than did similar extracts from normal renal tissue or from hypernephroma not associated with erythrocytosis. N. F. Jones and his associates[5] found that in two patients with non-neoplastic renal disease the erythropoietic activity of the plasma was initially raised and returned to normal after nephrectomy. Their method of bioassay by reticulocyte counts is less specific than other methods, but L. M. Rosenbach and E. D. Xefteris,[6] using a different technique, got similar results. It does seem probable, therefore, that the high red-cell counts which occasionally develop in patients with renal lesions, especially hypernephromas, result from the production of an excess of erythropoietin within the abnormal kidney. Thus, if a patient has renal disease, treatment is likely to relieve any accompanying erythrocytosis. Conversely, when a patient presents with erythrocytosis it is wise to look for a renal lesion. The reverse of this picture may perhaps be seen in the anaemia of renal insufficiency. It seems possible that the anaemia sometimes seen in patients with chronic renal disease may be due to defective production of erythropoietin.[24-26] If erythropoietin eventually becomes available for therapeutic use, it is in this form of anaemia, and perhaps also in the anaemia of chronic infection, that it is most likely to prove beneficial.

PROPERTIES OF INTERFERON

Interferon was first described by A. Isaacs and J. Lindenmann about four years ago.[1] They found that when tissue cultures of chick chorio-allantoic membrane were incubated with heat-inactivated influenza virus a substance with antiviral properties appeared in the fluid medium. This first observation of an antiviral antibiotic naturally aroused great interest and started active investigation into its nature and function. At a recent symposium in New York Isaacs[2] gave an account of the progress that has been made towards an understanding of its properties.

Interferon is a protein, slightly smaller than rabbit antibody globulin, with a molecular weight of about 63,000.[3] It does not appear to be antigenic, and in the tests so far carried out with both concentrated and crude specimens has shown no signs of toxicity. Moreover, it apparently does not interfere with the body's natural immunity mechanism.[4 5] Broadly speaking, interferon is produced when many different types of living cells (normal or malignant) are incubated with live or inactivated virus. It can be produced in kidney tissue, testis, amnion, lung, and chorio-allantoic membrane from human and monkey tissues as well as from chick, rabbit, and many other animal species. In their original work Isaacs and Lindenmann[1] used heat-inactivated influenza virus to stimulate production of interferon, but other forms of inactivation, particularly with ultra-violet light, are also effective. Live virus can also be used.[6] Interferon has been detected after infection of cells with several strains of influenza virus, measles, poliovirus, vaccinia, and vesicular stomatitis virus, and by one tumour virus, polyoma virus.[1] Some of the inhibitory substances so produced—for example, the virus inhibitory factor described by M. Ho and J. F. Enders[7] in human amnion cells infected with poliovirus, and the substance formed after infections of rabbit skin with vaccinia virus[8]—are probably closely related if not identical to interferon. The spectrum of antiviral activity appears to be wide. Thus both large viruses (vaccinia) and smaller viruses (poliovirus) are affected as well as many other R.N.A. and D.N.A. viruses. Indeed, the stimulation of cells to produce interferon and susceptibility to interferon may well prove to be a general property of viruses. Herpes simplex appears to be an exception; yields of interferon after incubation with this virus are low, and the virus appears to be insensitive to interferon.[9]

When it comes to measuring the effect of interferon, considerable cellular specificity becomes apparent. D. A. J. Tyrrell[6] has shown that chick interferon is more active when tested in chick cells than calf interferon and vice versa, and similar differences have been noted between mouse and ferret interferon and between human and monkey interferon. R. N. P. Sutton and Tyrrell[10] have shown that this cellular specificity may not be absolute, as they were able to demonstrate the inhibitory action of monkey interferon in both human and calf cells. This is a matter of some practical importance in the preparation of interferon for trials in human beings. Though interferon has many useful properties as a potential therapeutic substance in that it is non-antigenic, non-toxic even after concentration, and stable at *p*H2, it would be an advantage if production could be carried out in tissues other than human or simian to avoid the risk of contamination by latent viruses as well as on grounds of economy.

[1] Isaacs, A., and Lindenmann, J., *Proc. roy. Soc. B*, 1957, **147**, 258.
[2] —— *Perspectives in Virology*, 1960, Second Gustav Stern Symposium, published by Burgess Publishing Company, N.Y. P. 117.
[3] Burke, D. C., *Biochem. J.*, 1961, **78**, 556.
[4] Hitchcock, G., and Isaacs, A., *Brit. med. J.*, 1960, **2**, 1268.
[5] Ibid., 1960, **2**, 1371.
[6] Tyrrell, D. A. J., *Nature* (*Lond.*), 1959, **184**, Suppl. 7, 452.
[7] Ho, M., and Enders, J. F., *Virology*, 1959, **9**, 446.
[8] Nagano, Y., and Kojima, S., *C.R. Soc. biol.* (*Paris*), 1958, **152**, 1627.
[9] Cantell, K., and Tommila, V., *Lancet*, 1960, **2**, 682.
[10] Sutton, R. N. P., and Tyrrell, D. A. J., *Brit. J. exp. Path.*, 1961, **42**, 99.
[11] Quoted by Isaacs, A., and Baron, S., *Lancet*, 1960, **2**, 946.
[12] Isaacs, A., and Baron, S., ibid., 1960, **2**, 946.
[13] —— and Hitchcock, G., ibid., 1960, **2**, 69.

Additional information on the specificity of interferon is to be found in a report by Dr. R. D. Andrews in this week's issue of the *Journal* (p. 1728). Several batches of interferon (some of which were concentrated) prepared from rabbit, chick, monkey, human, and calf tissues were tested for their inhibitory effect against vaccinia virus in the rabbit's skin. Both interferon and virus inoculum were injected intradermally into the same site. When interferon was injected 24 hours before the virus, it was found to give protection. This was greatest with the homologous interferon (rabbit), but was also demonstrable with both monkey and chick interferons. When injected simultaneously as the challenge virus, the superiority of the homologous interferon was more striking. One batch of human-amnion interferon was also found to be as effective as monkey interferon. In one experiment in cynomolgus monkeys both chick and homologous interferon appeared to be highly effective in suppressing vaccinial infection, whereas one batch of rhesus monkey interferon gave considerably less protection. It looks, therefore, as if differences between interferons undoubtedly exist, but that these may be of less significance as improved methods of production and assay become available.

Some other interesting facts have also come to light. Ho and Enders[7] showed that poliovirus stimulated the production of interferon in HeLa (cancer) cells, but the assay could only be carried out in normal human kidney or amnion cells. Similarly, Chany[11] found that interferon produced in KB (cancer) cells could be assayed only in normal (non-cancerous) cells. Isaacs[1] has shown that interferon-treated cells show increased glycolysis, possibly as a result of an uncoupling action by interferon on oxidative phosphorylation similar to that of dinitrophenol. Neither interferon nor dinitrophenol show antiviral activity in HeLa cells. In a recent study Isaacs and S. Baron[12] found that embryonic cells from chick chorioallantoic membranes and from chick and mouse embryos produced less interferon than did more mature cells and were also considerably less sensitive to the action of interferon. In this latter respect embryonic cells behave like cancer cells. There is some experimental evidence[13] that interferon may play a part in aiding recovery by limiting infection, and Isaacs and Baron[12] have put forward the suggestion that the relative insensitivity of embryonic cells to interferon may perhaps serve to explain the susceptibility of the human foetus in the first trimester to rubella virus. This is a thought-provoking idea, but clearly the metabolic behaviour of normal, embryonic, and cancer cells in terms of interferon production and sensitivity will merit further study.

THE HENRY DALE PROFESSORSHIP

On his 86th birthday last week the Royal Society announced that Sir Henry Dale's name is to be associated with a professorship in medical research. The Wellcome Trustees have made a gift of £100,000 to establish and endow the professorship "to commemorate the unique services of Sir Henry Dale, O.M., G.B.E., F.R.S., to their Trust as its Chairman for 22 years as well as his outstanding contribution to science and medicine in a wider context."

The Council of the Royal Society expresses its satisfaction in being associated with the Wellcome Trustees in thus honouring one who served it as Secretary (1925–35) and as President (1940–45). This satisfaction will be warmly and widely shared by scientists and medical men all over the world. The appointments to the new professorship will be especially, but not exclusively, related to physiology and pharmacology—the field of Sir Henry's own great endeavour.

CONGENITAL DISLOCATION OF THE HIP

There is still no unanimity of opinion on the best type of treatment for congenital dislocation of the hip. Some years ago Denis Browne[1] wrote that with efficient conservative treatment in the early months of life the child with a congenital dislocation of the hip should develop like a normal infant. On the other hand, E. W. Somerville and J. C. Scott[2] suggested that conservative treatment should be abandoned and replaced by routine operations, because it had failed to produce the required results.

Two carefully compiled, large follow-up series have recently been published and help to throw some light on this difficult problem. One series of 149 cases was followed up by J. Wilkinson and C. Carter at the Hospital for Sick Children, Great Ormond Street.[3] All children were treated conservatively. In about half the cases the dislocation was reduced by manipulation under anaesthesia, in half by skin traction and gradual abduction. After reduction either the two limbs were put into plaster or a Denis Browne harness was applied. In older children the harness was preferred. In unilateral cases with a "normal" opposite acetabulum (these comprised more than half of the series) the results of conservative treatment were good; in unilateral dislocations with a shallow opposite acetabulum and in bilateral dislocations the results were on the whole unsatisfactory. All the children were under 4 years of age. Wilkinson and Carter's great contribution to the subject of congenital dislocation of the hip is their correlation of initial radiological findings and ultimate prognosis. They have shown that in

[1] Browne, D., in *Techniques in British Surgery*, 1950, edited by R. Maingot, p. 571.
[2] Somerville, E. W., and Scott, J. C., *J. Bone Jt Surg.*, 1957, 39B, 623.
[3] Wilkinson, J., and Carter, C., ibid., 1960, 42B, 669.
[4] MacKenzie, I. G., Seddon, H. J., and Trevor, D., ibid., 1960, 42B, 689.

unilateral dislocations the prognosis depends mainly on the angle of the slope of the opposite acetabulum.

In a series of 137 cases followed up in the Royal National Orthopaedic Hospital[4] H. J. Seddon and his colleagues found that conservative treatment was satisfactory in 58% of the children under the age of 3 years and occasionally in children under 5 years of age. The treatment of choice in this hospital was closed reduction on a frame. Open reduction had to be performed in 20% of the cases under the age of 3 years. In both series fragmentation of the femoral epiphysis occurred in 20 to 25% of the unilateral cases. In the Great Ormond Street series fragmentation occurred only in children whose hips had been reduced by manipulation. Seddon and his colleagues showed that in many cases the acetabular roof may fail to develop after reduction. In children under 12 years of age a preventive acetabuloplasty should be done. In older children and in those in whom the curvature of the acetabulum is normal but does not extend far enough laterally, a shelf operation should be performed.

The authors of both papers agree that treatment should be started as soon as the patient is seen. Unfortunately late diagnosis is still a major problem, and will remain so until "newborn babies were to receive as careful an examination as horses do before purchase."[1]

CHROMOSOME ABNORMALITIES AND CONGENITAL MALFORMATION OF THE HEART

In man the loss or gain of a single chromosome generally results in a multiplicity of abnormalities. As examples we need only recall the many clinical features which characterize Turner's syndrome and mongolism and to remember that, in both, heart disease is commonly found as one of the manifestations.

An interesting new development comes from Sweden, where P. Zetterqvist[5] has described a family containing eight certain and five probable cases of auricular septal defect in otherwise healthy individuals, the abnormality apparently being inherited as a dominant trait. J. A. Böök, B. Santesson, and P. Zetterqvist[6] have now examined the chromosomes of one family belonging to this pedigree and found that the affected mother was trisomic for a small chromosome of the 19–20 group. The chromosomes and the clinical state of the husband and the daughter were entirely normal, but the son proved most remarkable. Though symptomless, he was found to have a mild auricular septal defect, and in his karyotype he had the same trisomy as his mother, but in addition he was *monosomic* for chromosome 22, this bringing his total complement to the normal 46. Of several possible explanations the most likely is that the boy originated from an ovum which contained the extra maternal chromosome, but that this egg by nondisjunction had lost chromosome 22 because the additional chromosome of the 19–20 group had disturbed meiosis.

[5] Zetterqvist, P., *Acta paediat.* (*Uppsala*), 1960, **49**, 741.
[6] Böök, J. A., Santesson, B., and Zetterqvist, P., *Acta paediat.* (*Uppsala*), 1961, **50**, 217.

It is likely that this particular family is very unusual and that the great majority of patients with congenital heart disease (unassociated with other abnormality) will show a normal karyotype; in the rather few cases in which the chromosomes have been examined this in fact is so. Nevertheless, it is impossible to be dogmatic without examining more cases in the light of this new knowledge, and it will be particularly interesting to know the findings in other members of the Swedish pedigree.

ONSET OF STRESS INCONTINENCE

Over the last twelve years the Liverpool school have made a series of notable contributions to our knowledge of the physiology of micturition in the female and of the mechanism of its control, both when perfect and when impaired. The latest in this series is an investigation by Winifred J. A. Francis[1] into the time of onset of stress incontinence. She points out that, though this discomforting symptom has generally been regarded as due to the trauma of labour, it occurs also in nulliparous women. This point has been made before[2–4]: other workers have noted that about 50% of young nulliparae confess to stress incontinence of some degree, though usually slight and intermittent. Mr. H. P. Winsbury-White, in his most recently reiterated plea for urethrocystoscopy in the investigation of all forms of incontinence in the female,[5] has also stated that stress incontinence in nulliparae usually had its origin in infancy or childhood. In fact, a woman thus troubled might remain single and nulliparous because the intimacy of married life would disclose her embarrassment.

Dr. Francis questioned a random sample of 400 pregnant women and found that 268 (67%) admitted to some degree of stress incontinence during the current pregnancy—53% of the 222 primigravidae and 85% of the 178 multigravidae. These 268 women were subjected to cystometry, but endoscopy was not carried out. The outstanding conclusion reached from this research and from following up the 400 women through labour and puerperium was that stress incontinence rarely, if ever, appeared for the first time after childbirth. The symptom began either before the first pregnancy or during the first or a subsequent pregnancy, and every woman who had stress incontinence in the puerperium had suffered from it during the preceding gestation. Once manifested, the disability generally increased in degree in successive pregnancies and might then persist in the absence of pregnancy. Dr. Francis also carried out urethrocystography in late pregnancy in 33 women with stress incontinence and in 50 with normal control. The characteristic radiographic sign of loss of the posterior urethrovesical angle was seen in 30 of the 33 women with incontinence but in only 4 of the 50 women with good control of the bladder. Follow-up of these women and of others afflicted by stress incontinence during pregnancy showed

[1] Francis, W. J. A., *J. Obstet. Gynaec. Brit. Emp.*, 1960, **67**, 899.
[2] Nemir, A., and Middleton, R. P., *Amer. J. Obstet. Gynec.*, 1954, **68**, 1166.
[3] Duncan, A. S., quoted by Kellar, R. J., *Proc. roy. Soc. Med.*, 1956, **49**, 657.
[4] Kennedy, C., *Brit. med. J.*, 1960, **2**, 263.
[5] Winsbury-White, H. P., *Proc. roy. Soc. Med.*, 1960, **53**, 1016.

that within a few days of delivery nine out of ten women previously troubled regained good control of the bladder, even though *x* rays showed no restoration of the lost angle; that is, functional cure preceded anatomical return to normal. Further studies to ascertain how long it took for the angle to return, in those cases in which it did return, were not carried out because of the possible risks from the irradiation.

This investigation therefore has produced valuable evidence that women do not develop stress incontinence because of the strains of labour, but that those who suffer from this discomfort in later life are destined from an early age to do so, and that pregnancy, not labour, commonly reveals or aggravates an intrinsic defect in their sphincter mechanism.

KERNICTERUS AND PREMATURITY

In considering how prematurity, hyperbilirubinaemia, and kernicterus are interrelated, some established facts may usefully be set out. The reason why many premature infants develop jaundice after birth is because they have a relative lack of glucuronyl transferase in the liver (or possibly because of the inhibition of this enzyme). Consequently bilirubin in the unconjugated state accumulates, for unconjugated bilirubin cannot be excreted by the liver.[1] Hyperbilirubinaemia is liable to be increased by administration of vitamin-K analogues, which, if given in other than low dosage, may cause haemolysis.[2] Kernicterus may develop in premature as in other infants if the plasma bilirubin reaches high levels. Kernicterus is rare with levels under 20 mg. per 100 ml.; it is common but still not invariable with levels of over 30 mg.; there is much difference of opinion on its incidence in the intermediate range of 20 to 30 mg.[3] The hazard of kernicterus is increased by the presence of various substances which compete with bilirubin for binding-sites on albumin; such substances include salicylates and sulphonamides,[4] and the latter may reach the infant from the use of long-acting sulphonamides given to the mother some time before parturition.[5]

Recently a further factor, deficiency of glucose-6-phosphate dehydrogenase (G-6-PD), has been added to an already complex situation. Red cells lacking this enzyme are sensitive to the effects of various substances, including primaquine, water-soluble vitamin-K analogues, naphthalene, and the fava bean, so that individuals with the enzyme defect may develop haemolytic disease if exposed to these substances. The part played by deficiency of G-6-PD in neonatal jaundice is not yet clear, but it is likely to vary greatly according to the racial group concerned, since this inherited defect, rare in Great Britain, is relatively common in some races such as Negroes. In a study of the subject by S. A. Doxiadis and others[6] in Athens one case of G-6-PD deficiency was discovered among a group of twenty premature infants with severe hyperbilirubinaemia. (The defect was present in as many as ten of seventeen full-term infants with unexplained severe hyperbilirubinaemia.)

The incidence of kernicterus of prematurity shows extraordinary variations from centre to centre,[3] or even in one centre at different periods. One centre reported that 60% of all premature infants in whom the plasma bilirubin exceeded 18 mg. developed kernicterus,[7] whereas some centres have never seen a case. Known exogenous factors, such as vitamin K and sulphonamides, may partly explain such variations, and other as yet unrecognizable exogenous factors may affect the foetus, when we recall the variety of drugs—vitamins, haematinics, hypnotics, analgesics, anaesthetics, oestrogens, and oxytocics—that the pregnant woman of to-day is liable to receive. In a recent study from Chicago,[8] 122 premature infants, none of whom had had an exchange transfusion, were followed up for a year and assessed for evidence of neurological damage. Three cases of kernicterus developed; all three were in a small group of eight cases in which the bilirubin level had exceeded 30 mg. By contrast, of the 37 cases in which the bilirubin had risen to between 20 and 30 mg. none developed kernicterus. Most of the babies in this series were Negro, and this fact alone makes it impossible to assume that the incidence of kernicterus would be similar elsewhere.

Exchange transfusion, apart from often proving a disappointingly temporary means of lowering the plasma bilirubin level, is not lightly to be undertaken in a small premature infant several days old, where the umbilical route may no longer be available. When the bilirubin level in a premature infant rises to 20 or 25 mg., therefore, it is an exceedingly perplexing matter to weigh up the pros and cons of exchange transfusion. It is earnestly to be hoped that some means more satisfactory than exchange transfusion may soon appear for dealing with neonatal hyperbilirubinaemia and its consequences.

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MORE AND MORE PEOPLE

The preliminary reports[1] from this year's census of the British Isles confirm that the total population has again increased, as the intercensal estimates had predicted. In the last year or so an important part of the increase has been due to immigration, but in the period 1951–61 as a whole much the greater part has been the result of an increasing birth rate combined with a falling death rate at young ages. Yet the outcome of these changes is not easy to forecast precisely, because the higher birth rate seems to be mainly the consequence of a fall in the average age of marriage. In other words, in this period of transition some people have not waited as long as they would formerly, so that they get married alongside others who have waited. The result is an increase in the number of marriages and hence of children, but if the ultimate size of the family remains the same the effect on the total population will be seen as a bump in the graph rather than an upward tilt to the sky.

[1] See p. 1772. [2] *Brit. med. J.*, 1960, **2**, 1941.

In the British Isles the greatest increase in population since the 1951 census has been in England and Wales, and most notably in south-east England. As this country is already one of the most densely populated in Europe, the question how many more people it can adequately support is being anxiously asked. But the problem in our islands is overshadowed by the population explosion outside them. At present a net increase of about 48 million to the world's population is expected every year —or more than the whole population of England and Wales.[2] This net increase is itself likely to become much bigger. With a regional rate of population increase in Northern and Western Europe of 0.6% a year, the following rates from areas where they are high may be compared: Central America 2.7%, South-west Asia 2.5%, South America 2.3%, Oceania 2.3%, South-east Asia 2.1%, and Northern Africa 2.1%. The threat that this kind of expansion can be in a limited area is discussed by Dr. Ffrangcon Roberts in a stimulating article at p. 1750 of the *Journal* this week. In Mauritius, he reports, the annual increase in population is 3.38% ; at that rate the population will be doubled in 1978. Whether disaster, or at least "terrible hardship," can be averted seems questionable to Roberts, as it has done to other observers of the wider scene in the world as a whole. Even if the human species retains sufficient control over its aggressive instincts to prevent a catastrophe, can its reproductive instincts be curbed to avoid "terrible hardship"? Medical men have an important contribution to make to this crucial problem of our time.

BIRTHDAY HONOURS

The knighthood conferred upon Dr. H. Guy Dain "for services rendered to the B.M.A. and the G.M.C." will be applauded far and wide by two generations of members of the B.M.A. His services to the Association, and so to the medical profession—somewhat belatedly recognized in his 91st year—have been many and varied. He became a member of the Insurance Acts Committee as far back as 1917, and in 1924 succeeded as Chairman of the Committee that other great B.M.A. figure, Sir Henry Brackenbury. Dain came to the height of his power and influence as Chairman of the B.M.A. Council from 1943 to 1949. His period of office coincided with the revolution in medical services heralded by the Beveridge report of 1942 and completed by the introduction of the N.H.S. in 1948. Throughout these stormy and controversial years his skill as a negotiator and power of logical and persuasive presentation of the facts of the case prevailed over the turmoil of conflicting counsels. It was Dain's dogged persistence that made the Government agree in 1948 to introduce the amending Act which safeguarded the profession from the arbitrary introduction of a whole-time salaried service. His multitude of friends and admirers will wish him many years in which to enjoy the honour he has so richly deserved.

Professor A. Bradford Hill, it is of interest to recall, gave the Association his expert help as a statistician in determining the basis of remuneration for G.P.s and consultants in the two historic Spens Reports. This might be described as a side-effect of the work of one who, though not a medical man, has probably had as great an influence on the development of medical science, and indeed practice, as anyone else of his generation. His papers with Doll on the causal connexion between smoking and lung cancer alone give him his place in the history of medicine. But his work in the design of clinical and prophylactic trials, and in their execution, has altered the whole approach of the modern doctor to the problems of medicine. Following the example of his predecessor, the late Professor Major Greenwood, Bradford Hill has taught the clinician how to measure the effects of drug therapy and prophylactic vaccines. His knighthood will be welcomed the world over as a fitting recognition of his influence as a scientist who has spent his life working with and teaching doctors.

The knighthood awarded to Professor C. F. W. Illingworth, regius professor of surgery in the University of Glasgow, honours one who is both a distinguished surgeon and an outstanding teacher. His work on peptic ulcer in particular has won him an international reputation, while his textbooks and instructional articles (a number of which have appeared in this journal) have notably helped readers, by their clarity and common sense, to share the wide experience on which they are based. At Glasgow generations of students have been grateful for the personal attention he has given to their welfare.

Two medical civil servants are honoured for their enthusiastic and often little acclaimed labours. Dr. J. C. R. Buchanan becomes K.C.M.G. for his work at the Colonial Office, of which he has been Principal Medical Officer since 1948. Much of his professional life was spent serving the welfare of the African Colonies. Dr. C. G. Magee's devoted services to medicine at the Ministry of Pensions and National Insurance are fittingly rewarded by a knighthood. A K.C.B. has been conferred on Mr. B. D. Fraser, who last year became Permanent Secretary at the Ministry of Health.

The honour of a barony conferred on Sir Simon Marks, Hon.F.R.C.S., will be acclaimed by surgeons everywhere, for his personal benefactions were of immense help in the rebuilding of the Royal College of Surgeons and the construction of its new scientific departments.

It is also a pleasure to note the names of two Australian surgeons among the new knights. They are Dr. R. F. Matters, a distinguished obstetrician of Adelaide, and Dr. I. D. Miller, until lately President of the Royal Australasian College of Surgeons.

Other medical men in the Honours list, on whom the C.B.E. is conferred, include Dr. Desmond Curran, of St. George's Hospital, recently appointed professor of psychiatry there ; Dr. A. Rae Gilchrist, immediate Past-President of the Royal College of Physicians of Edinburgh ; and Professor J. Chassar Moir, the distinguished obstetrician, of Oxford.

CONTROL OF POPULATION

PANACEA IN TWO ISLANDS

BY

FFRANGCON ROBERTS, M.D.

In the early years of this century it became obvious to demographers that the population of Western Europe was increasing only because of longer survival, and that if the continuing fall in the birth rate was not reversed a decline was inevitable. This prediction was most forcibly expressed by Spengler (1917), who saw in this "metaphysical turn towards death" a portent of the eventual extinction of Western civilization. Many British writers supported Spengler's contention. During the first world war public meetings were held urgently advocating the production of more children, but a people disillusioned as to the worth of human life by the holocaust then occurring on the Western Front received this exhortation with cynical derision.

Great Britain

After the war the birth rate in Great Britain continued to decline. In his Annual Review, 1926, the Registrar-General for England and Wales wrote: "It seems extremely probable that since about 1923 the birth rate in this country has entered upon a stage which, if no further improvement takes place, must eventually result in a declining population. On the other hand, if, as is quite possible, the present lowness of the birth rate is only a temporary phenomenon reflecting the prolonged economic depression of the post-war period, the tendency may be corrected before the consequential decline actually sets in, while even in the most extreme circumstances it could hardly commence for some decades to come."

In 1939 the Government, in order to allay public anxiety, issued a Memorandum (CMD 6358). This indicated that the population of Great Britain, which stood at 46 millions in 1937, would increase to 47.5 millions in 1951 and would then decline to 46.0 in 1971 (Fig. 1, A). At the same time it believed that the pessimistic distant forecasts which had been made in certain sensational and well-publicized articles were not justified. This Memorandum was subsequently reissued as a White Paper, *The Current Trend of Population in Great Britain*; it formed the basis of the Beveridge Report on *Social Insurance and Allied Services*, 1942.

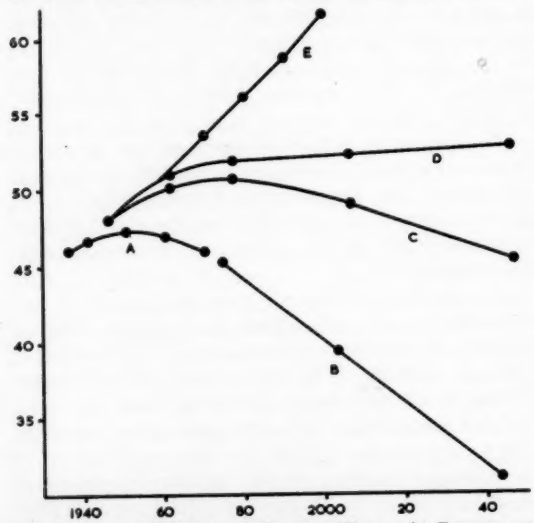

FIG. 1.—Great Britain, population in millions. A, Government Memorandum, 1939. B, P.E.P., 1948. C, Royal Commission on Population, 1949, assuming a continuation of existing family size. D, Royal Commission on Population, assuming a 6% increase in family size. E, Registrar-General's projection for England and Wales (1960), to which one-ninth has been added for Scotland.

The prospects thus disclosed led to the appointment, in 1944, of the Royal Commission on Population. Its terms of reference were to examine existing population trends, their causes and probable consequences, and to consider what measures, if any, should be taken to influence them. In other words, it was directed not only to examine future trends but also to determine the optimum population—that is to say, the population best suited to the country's economic situation. In its report, published in 1949, the Commission, basing its calculations on a continuation of the average family size of 2.2 (the number of children in completed families) and of the marriage rate existing between 1929 and 1938, predicted a rise from 48.2 millions in 1947 to a maximum of 50.7 in 1977 followed by a fall to 48.9 in the year 2007 and 45.5 in 2047 (Fig. 1, C). The Commission was therefore less pessimistic than the Memorandum both as to the maximum and as to the time-relations, but agreed that an eventual fall was inevitable.

Meanwhile, in 1948, the voluntary organization known as P.E.P. (Political and Economic Planning) published its *Population Policy in Great Britain*. Basing its calculations on a continuation of the fertility rate existing in 1938–9, it predicted a reduction in the population of England and Wales from 42.4 millions in 1944 to 28.0 in the year 2044. The addition of one-ninth for Scotland (a sufficiently accurate approximation) gives 31.1 for Great Britain in 2044 (Fig. 1, B)—a far more pessimistic projection than that of the Commission, and one that supported the gloomy prognostications of earlier writers.

To return to the Commission. To the assessment of the optimum population the Commission gave very full consideration. Recognizing that it depended on foreign trade and admitting that the trend of foreign trade was difficult to forecast, the Commission believed that the balance of payments was likely to be stabilized at a slightly higher level than then existed. Future needs would accordingly be best met by an increase in population to a level slightly higher than the predicted maximum of 50.7 and by stabilization at that level. The population ideally suited to the economy was one that would rise to 51.8 millions in 1977 and thereafter continue to rise slowly to 52.3 in 2007 and 52.7 in 2047. This would be achieved if family size were raised by 6%—that is, from 2.2 to 2.33 (Fig. 1, D).

In order to stimulate the required increase in family size the Commission made recommendations of two kinds: financial inducements to parenthood and measures for the better conservation of life from the moment of conception. Financial inducements consisted in an increase in the marriage and children's allowances which had been instituted in 1946 and an increase in income-tax relief depending on the number of children. These recommendations were substantially implemented by subsequent budgetary provisions. Measures for the conservation of life consisted in better housing with rent subsidies; greater provision of domestic help, nurseries, nursery schools, baby-sitters, laundry facilities, and holidays for mothers; the further

development of health and maternity services; more midwives; the establishment of convalescent and rest homes for mothers; courses of instruction in child health; and the prosecution of research into the causes and treatment of involuntary childlessness. The recommendations also included instruction in contraception. This apparent paradox is explained by the fact that such instruction was designed, not to limit families, but to secure greater survival of infants by better spacing of births.

By the time that the Commission's report was published many of its medical and social recommendations had been initiated by the Ministry of Health and were being more fully developed under the National Health Service, which had come into force in 1948. It thus came about that two movements affecting population were being set in train simultaneously and independently but with objects that were fundamentally different. On the one hand, the Commission, though taking social justice into account, was concerned solely with the attainment of an optimum population in the national interest, relying largely on improvement in health. On the other hand, the National Health Service was concerned solely with the promotion of health irrespective of population requirements, although the Beveridge Report, on which the Service was based, had called attention to the impending decline in population. There was, however, a connecting link in that improvement in the treatment of certain forms of ill-health might be expected to increase productive efficiency and thus enable the country to support a larger population.

The sequel is surprising. The birth rate continued to fall until 1955, but since then has shown a remarkable and progressive rise. According to the latest projections the population will be nearly 62 millions at the end of the century, a figure far higher than the Commission expected even in the most favourable circumstances. Within five years the situation has thus been completely transformed. The threat of depopulation has vanished for at least a hundred years, and in its place is the certain threat of overpopulation. Although psychological factors such as an altered attitude to parenthood cannot be excluded it may be presumed that the rise in the birth rate is due partly to the great increase in national prosperity (which the Commission could not have foreseen), but mainly to the establishment of conditions more favourable to the rearing of families. The result shows that the adjustment of population to economic conditions (which are themselves as unstable and unpredictable as human behaviour) is beyond the power of man to accomplish.

Mauritius

In Great Britain it thus happened that the need for a larger population and the need for better national health coincided and called for the same measures. But things might have been otherwise. What would the Commission have recommended had it found that the country was overpopulated, and, so far as could be seen, in perpetuity? Would it still have advised medical and social measures designed to improve health? Would it have advocated instruction in contraception with the object not of the better spacing of births but of their reduction? Some indication may be gained by the revelation of conditions in Mauritius. Owing mainly to the suppression of malaria the population of that island, which is now 600,000, or 835 to the square mile, has increased by 50% since 1945. Concerned at the prospect, the Governor commissioned two Reports, which have now been published. The one, by Professor J. E. Meade and others (1961), deals with the social and economic structure of the island; the other, by Professor R. M. Titmuss and others (1961), deals with population growth and social policies. The Reports agree that the future of the island is menacing in the extreme. They calculate that if the existing fertility rates continue and if mortality rates decline owing to improvements in health and medical care the population will be more than doubled by 1982 (Fig. 2, A). Since

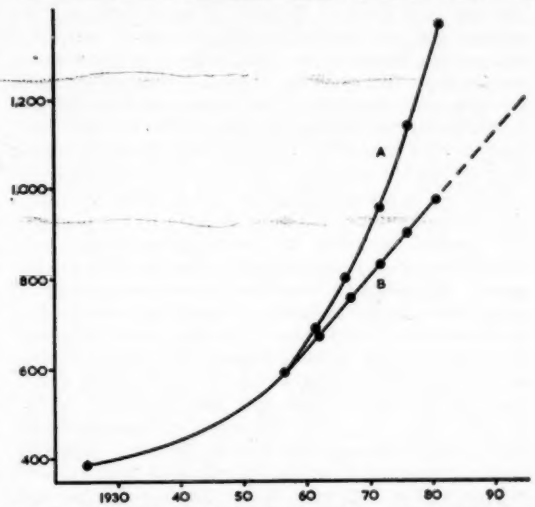

FIG. 2.—Mauritius, population in thousands. Continuous lines constructed from data in the Titmuss report; interrupted line added by the writer: A, assuming a continuation of existing fertility rates; B, assuming the drastic adoption of family planning. In both it is assumed that mortality will decline owing to improved medical care.

opportunities for economic expansion are limited, and no relief can be expected from emigration, a drastic slowing down of population growth is the only means of saving the people from certain catastrophe.

The recommendations made by Titmuss and his associates are of two kinds: the improvement of social and medical care and the adoption of family planning. The first of these includes the establishment of social insurance and public assistance, the development of preventive health and welfare services (most urgently needed in maternity and child welfare, which are very backward), free admission to hospitals, a free salaried family-doctor service with inducements to doctors to work in rural areas, and an increase in the number of doctors together with a raising of ethical medical standards. Family planning, serviced by charitable organizations, should aim at the limitation of families to three children. Spaced families should be given financial support. Allowances should not be given after the third child. Late marriages should be encouraged.

It will thus be seen that although the problems facing the two countries are diametrically opposed—in Great Britain threatened depopulation (as seen in 1944), in Mauritius threatened overpopulation—the remedies suggested are substantially the same. Diametrically opposed, too, are the purposes of family planning—increase in family size in Great Britain and decrease in Mauritius. We are, moreover, dealing in the one case with a sophisticated society that has learnt to regulate procreation according to its wishes for the last 80 years,

and in the other case with a primitive society where such knowledge does not exist.

The question therefore arises: which of the two remedies proposed for Mauritius is the more likely to be effective—the medical and social measures which in Britain have been followed by a striking increase in population, or family planning which is intended to reduce population? In the light of British experience the answer can hardly be in doubt. The low standard of medical and social services now existing in Mauritius provides immense scope for improvement on a scale that does not exist in Britain. The initiation of the reforms will no doubt be difficult, more especially because the islanders pin their faith in magical forms of medicine. But when the efficacy of modern medicine becomes visible substantial improvement in health and survival may be confidently expected. On the other hand, in view of the low cultural standard of the people the need for contraception will be difficult to instil, and instruction in the technique will be difficult to impart. This will take time, but time is against the planners. The general adoption of contraception must begin immediately if it is to have any effect in the next few years. A complete revolution in *mores* overnight is more than can be expected. Moreover, one-third of the population are Roman Catholics, and the priests have lost no time in condemning the proposal. Nor is the experience of other countries encouraging. Puerto Rico has reduced its birth rate only from 40.5 to 31.5 in eight years. In India the result of a campaign for birth control costing £3m. has so far been negligible. Only in Japan has a substantial reduction been achieved —from 34.3 in 1947 to 17.2 in 1957—but this has been mainly due to voluntary sterilization and abortion. In 1956 there were 1,160,000 sanctioned abortions.

The withholding of allowances after the third child is of doubtful value, since allowances for three children are better (for the parents) than none at all. As to the encouragement of late marriages, it is difficult to see how this can be achieved without penalizing early marriages. In this matter comparison with the Republic of Ireland is relevant. That country enjoys the distinction of having the highest proportion of bachelors in the world. This is because, the farms being no longer divisible, only the eldest son can inherit, and even he has to wait until his father dies. Restraint from marriage has therefore arisen voluntarily, for the men have always before their eyes grim evidence of their limited prospects. Such considerations would hardly weigh with paid workers on sugar estates.

The most that is expected from these proposals is a reduction of the annual increase in population from 3.38 to 2.03%. At the existing rate population will be doubled by 1978; with the general adoption of family planning it will be doubled by 1995, a gain of only 17 years (Fig. 2). The implementation of the proposals will no doubt be of great benefit to the health of the community, but as a means of retarding population-growth it hardly seems worth while. Nothing short of complete arrest will save the island from catastrophe.

Comparison of Britain and Mauritius, countries so widely different in culture and resources, shows that the adjustment of population to economic conditions is equally difficult whether an increase or a decrease is required. The problem of course affects the whole world, as we are reminded almost daily, but it is easier to visualize in islands, especially those that cannot save the situation by foreign conquest. We see once more that control of the death rate can in the long run be of no advantage unless accompanied by control of the birth rate. Titmuss and his colleagues, of course, realize this; they go to the length of saying that if family planning is not accepted they would prefer to see their medical and social proposals rejected. They thus echo the view expressed by Myrdal (1957) that "measures for the rapid spread of birth control should be made part of the economic planning of under-developed countries." That medical benefits should in any circumstances be withheld is considered to run counter to the great traditions of medicine, but the grim future may force us to change our views. For, after all, death from disease may be no worse than death from starvation. There is no escape from the spectre of Malthus, who, it will be remembered, aroused violent antagonism through his objection to the Poor Law.

Viewing the problem from a distance, and while wishing a happy issue to the proposals made for Mauritius, one cannot help feeling that conditions will get worse before they are better, that only the experience of terrible hardship will teach the people the way of salvation.

Summary

In Great Britain measures designed to counteract the threat of depopulation have resulted in or at least been followed by the threat of overpopulation. Measures very similar to these are now proposed in order to counteract the threat of overpopulation in Mauritius. It would seem that their effect will be to stimulate rather than retard the growth of population, and that only the experience of extreme hardship will teach the Mauritians to adopt birth control.

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BIOCHEMISTRY OF HUMAN CANCER

INTERNATIONAL CONFERENCE IN LONDON

[FROM A SPECIAL CORRESPONDENT]

During the last three days of May a conference on the biochemistry of human cancer was held in the new conference hall at the Chester Beatty Research Institute of the Institute of Cancer Research. It brought together surgeons, clinicians, and pathologists with experimental scientists, including biochemists, morphologists, chemotherapists, geneticists, and immunologists. Of the forty-odd participants, nearly half came from abroad, including W. Rundles and C. Heidelberger from the United States, who came to establish liaison with a similar group which had met last year at Madison (U.S.A.), L. F. Larionov from Moscow, C. de Duve and J. Maisin from Louvain, Belgium, and others from Germany, Holland, Italy, Sweden, and Switzerland. The conference, organized on an informal basis without set papers, aimed by joint discussion to examine and extend the application of biochemical methods to human cancer, and to see how such methods could help in diagnosis and therapy.

Proposed Tumour Bank

The problem of the availability of human tumour material that has dogged work in this field was tackled by R. W. RAVEN (Royal Marsden Hospital) at the outset of the meeting, and he has agreed to convene a group who will aim to establish in London a bank of frozen tumour material obtained and kept under standard conditions and subjected to close histological control. This should be a very valuable contribution towards establishing much closer working relationships between medical and experimental workers in this field.

In spite of the title of the meeting, it was clear that only a relatively small amount of work has so far been done experimentally on the biochemistry of *human* cancer; perhaps a general effect of the meeting may prove to be a shift in the emphasis of biochemical research away from animal studies towards the admittedly more difficult field of human material that will become available from biopsies and excised tumours. C. I. COOLING (London) gave numerous examples of excised tumours he could have provided in the recent past. Just how difficult this work is likely to prove was indicated by the pathologists, who stressed the wide variability that was found between tumours of similar origin and even within one tumour. Undoubtedly the search for enzymic and metabolic abnormalities will require highly specialized techniques. The established biochemical techniques have been worked out generally on tissue homogenates from animals, and reliance has been placed on at least a statistical homogeneity of the tissue. Micro-techniques are indicated now if the much less homogeneous human tumour material is to be satisfactorily studied, and a good deal of discussion centred on such methods.

Micro-assay of Tumour Enzymes

B. SYLVEN (Stockholm) described his technique of micro-assays done on mouse mammary carcinoma. The deep-frozen tissue was sampled by punching out a cylinder of 1.5–3 mm. in cross-section, which could then be sectioned transversely or longitudinally. Individual transverse sections of 0.01 mm. thickness which contained 20,000–25,000 cells could be assayed separately for a variety of enzymes, and in animal tissue of this character the assumption of homogeneity in each section was supported by histological control. 1 mm. of the tissue cylinder would provide material for 100 serial assays, and the variation in enzyme activity from the growing tumour edge into the necrotic core could be studied. It was clear, however, that even this level of assay might be too gross, and histochemical methods received considerable attention. R. HESS (Basle) described the active staining of fresh frozen sections of human tumours. In all, some 45 different tumours, including eight cervical tumours, had been examined for acid-phosphatase activity, amino-peptidases, and oxidative enzymes including succinic and lactic acid dehydrogenase. No clear-cut differentiation had emerged by which malignant cells could be characterized routinely, but as a research tool the technique promised valuable information about the discrete biochemistry within tumour tissue.

Cytochemical staining of blood smears was shown by F. G. J. HAYHOE (Cambridge) to be a working diagnostic aid. Alkaline-phosphatase activity measured semi-quantitatively from the number and intensity of stained neutrophils was capable of providing a method of discriminating between the chronic leukaemias, Hodgkin's disease, and lymphosarcoma. Consecutive P.A.S.-staining could be used to reveal a characteristic pattern of glycogen in vacuoles in the lymphocytes in chronic lymphocytic leukaemia. Such techniques were also a guide to therapy, for smears that showed strong P.A.S.-staining often indicated good remissions.

Destruction by Enzyme Release

At a subcellular level, attention was focused on the role and structure of lysosomes within the cell. C. DE DUVE (Louvain) considered ways in which lysosomes present in a malignant cell might be induced to rupture and so release their content of hydrolytic enzymes, which might then produce autolysis and cell death. Although he was not optimistic about the practical application of methods of releasing the enzymic activity such as by lowering of *p*H, supersonic vibration, or lecithinase treatment, Miss HONOR FELL'S (Cambridge) work on the effect of vitamin A on embryonic cultures seemed hopeful. She reported her studies of the effect of culturing long-bone rudiments from mouse embryos in media containing vitamin A. Within six days the cartilage matrix was reduced and metachromasia had disappeared. The effect resembled that observed by LEWIS THOMAS (New York) using papain protease, and joint studies had subsequently suggested strongly that the vitamin A was achieving its effect by causing release of enzymes from the lysosomes. The morphological disposition of lysosomes was described by E. H. MERCER (London), whose electron-microscope studies had revealed the presence of lysosome-like bodies in epidermal structures that exfoliate, implying their function in the disintegration of the tissue. In the later discussions on the invasiveness of malignant cells—almost the only characteristic common to all tumours—it was suggested that, in a similar way, lysosomal enzymes might help the invasion.

Another characteristic of anaplastic tumour cells, described by E. J. AMBROSE (London), was their complete loss of contact inhibition in tissue cultures. This effect seemed to be related to the action of a non-enzymic, dialysable factor obtained by B. SYLVEN (Stockholm) from the interstitial fluid of mouse tumours. Within a few minutes of its addition to fibroblasts growing in culture the cells rounded up and became detached from the glass. Red blood cells and tumour cells did not react to the factor, which has been identified as a small-sized lipid associated with a polypeptide.

Isoenzyme Patterns

Miss D. CAMPBELL (London) reported the application of electrophoresis on a starch gel to serum alkaline-phosphatases, which were thus separated into their protein components—isoenzymes. The patterns of isoenzymes in the serum were characteristic both of organs and of pathological conditions. Thus a determination on the serum of a patient with mammary carcinoma had given a value characteristic for bone, indicating that the source of the serum alkaline-phosphatase was the bone secondaries. The technique appeared capable of giving assistance both in diagnosis and in following the development of a malignant growth by studying changes in the isoenzyme pattern.

During the discussion on metabolic pathways in human tumours, W. LÜHRS (Berlin) described the clinical application of triiodothyronine and chlorpromazine which had been shown in animal experiments to act as uncoupling agents of phosphorylation and respiration. These substances had the effect of eliminating drug-resistance, and patients with, for example, mammary carcinoma who had become unresponsive to oestrogen therapy began to respond again after administration of triiodothyronine. A patient with lymphatic leukaemia who had become resistant to T.E.M. (tretamine), after treatment with triiodothyronine required only 7 mg. of T.E.M. to go again into remission for more than one year.

At the end of the conference, apart from the plan for a human tumour bank referred to earlier, an informal committee agreed to meet periodically to collate baseline data on human tumour material and to encourage by exchange of information on an international scale the development of the many ideas and techniques discussed in the conference into practical biochemical studies. F. BERGEL and L. A. ELSON (Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, London S.W.3) have accepted responsibility for convening this committee, and all who are interested should contact them for further information.

BIRTHDAY HONOURS

The following names were included in the Birthday Honours List published on June 10.

K.C.M.G.

JOHN CECIL RANKIN BUCHANAN, C.M.G., M.D., F.R.C.P.Ed., F.R.A.C.P., D.T.M.&H. Medical Adviser to the Secretary of State for the Colonies.

Knighthood

HARRY GUY DAIN, Hon.M.D., Hon.LL.D., F.R.C.S. For services to the British Medical Association and the General Medical Council.

AUSTIN BRADFORD HILL, C.B.E., Ph.D., D.Sc., F.R.S. Professor of Medical Statistics, London School of Hygiene and Tropical Medicine, University of London.

CHARLES FREDERICK WILLIAM ILLINGWORTH, C.B.E., M.D., Ch.M., F.R.C.S.Ed., F.K.F.P.S., Hon.F.R.C.S., Hon.F.A.C.S. Regius Professor of Surgery in the University of Glasgow. Honorary Surgeon to the Queen in Scotland.

CUTHBERT GAULTER MAGEE, C.B.E., F.R.C.P.Ed., D.P.H. Chief Medical Officer, Ministry of Pensions and National Insurance.

REGINALD FRANCIS MATTERS, V.R.D., M.D., M.S., F.R.C.S.Ed., F.R.A.C.S., F.R.C.O.G. Honorary Consulting Obstetrician, Queen Victoria Maternity Hospital and Queen Elizabeth Hospital, Adelaide, and Honorary Consulting Gynaecologist, Royal Adelaide Hospital, South Australia.

IAN DOUGLAS MILLER, M.B., F.R.C.S., F.R.A.C.S. Past-President of the Royal Australasian College of Surgeons. Honorary Surgeon, St. Vincent's Hospital, Sydney, New South Wales.

C.B. (Civil Division)

NEVILLE MARRIOTT GOODMAN, M.D., Ph.D., F.R.C.P., D.P.H. Deputy Chief Medical Officer, Ministry of Health.

C.M.G.

JOHN ORDE POYNTON, M.D. Director of the Institute of Medical and Veterinary Science, South Australia.

C.B.E. (Military Division)

GEORGE HENRY MORLEY, O.B.E., F.R.C.S. Air Commodore, R.A.F. Honorary Surgeon to the Queen.

WILLIAM JAMES MEREDITH SADLER, M.R.C.S., L.R.C.P. Surgeon Captain, R.N. Honorary Surgeon to the Queen.

C.B.E. (Civil Division)

PAUL WILSON BRAND, M.B., B.S., F.R.C.S. Principal of the Christian Medical College and Hospital, Vellore, South India.

RICHARD DESMOND CURRAN, M.B., F.R.C.P., D.P.M. Senior Psychiatrist, St. George's Hospital, London, and Professor-designate of Psychiatry at St. George's Hospital.

ANDREW RAE GILCHRIST, M.D., F.R.C.P., Hon.F.R.A.C.P. Immediate Past-President of the Royal College of Physicians of Edinburgh. Physician and Consultant in Cardiology, Edinburgh Royal Infirmary.

JOHN CHASSAR MOIR, M.D., Hon.LL.D., F.R.C.S.Ed., F.R.C.O.G. Nuffield Professor of Obstetrics and Gynaecology in the University of Oxford.

JOHN JOSEPH POWER, D.S.O., M.B., Ch.M., F.R.C.S.Ed., F.R.A.C.S. A prominent surgeon of Brisbane, Queensland, Australia.

CHARLES HERBERT ST. JOHN, M.B., B.S., D.O.M.S. For public services in Barbados.

MARIE HILDA STEVENSON-DELHOMME, L.R.C.P.&S.Ed. For public services in Seychelles.

GEORGE WILLIAM HUGHES TOWNSEND, M.B., B.Ch., D.P.H., D.P.A. County Medical Officer and Chief Welfare Officer, Buckinghamshire County Council. Honorary Physician to the Queen.

CLIVE WENTWORTH UHR, M.B., Ch.M., of Clayfield, Queensland, Australia. For services to charitable organizations.

ROBERT SHARPE VENTERS, M.B., Ch.B., F.R.C.S.Ed. Chairman, Special Area Committee, Newcastle Regional Hospital Board.

M.V.O.

WILLIAM D'AUVERGNE MAYCOCK, M.B.E., M.D.
LEONARD RODYN, M.D.

O.B.E. (Military Division)

EDWARD SIDNEY ELLIOTT, B.M., B.Ch. Surgeon Commander, R.N.

DAVID IVOR FRYER, M.B., B.S. Squadron Leader, R.A.F.

O.B.E. (Civil Division)

OLADELE ADEBAYO AJOSE, M.D., D.P.H. Professor of Preventive and Social Medicine, University College, Ibadan, Western Region, Nigeria.

BARTHOLOMEW OSCAR BARRY, F.R.C.S.Ed., D.T.M.&H. Consultant Surgeon to Princess Tsahai Memorial Hospital, Addis Ababa, Ethiopia.

RALPH MARSHALL BATES, F.R.C.S., D.P.M. Medical Superintendent, Royal Eastern Counties Hospital, Colchester.

MARGARET STOTE GLEN BOTT, M.B., B.S., F.R.C.O.G., J.P. For public services in Nottingham.

MARC ANTOINE EMILE DUVIVIER, M.B., B.S. For public services in Mauritius.

KATHARINE ANNIS CALDER GILLIE, M.B., B.S., M.R.C.P. General Practitioner, Paddington, London.

NICHOLAS GREWAL, M.Ch.Orth., F.R.C.S.Ed. Senior Surgeon, Medical Department, British Guiana.

DAVID LOWRY HARBINSON, M.B., B.Ch., D.P.H. Medical Officer, Ministry of Health.

NORMAN DAVIDSON LAIRD, M.B., B.Ch., D.P.H., J.P. For political services in Belfast.

WILLIAM ANDERSON MURRAY, M.D., F.R.C.P.Ed., D.P.H. Consultant Chest Physician, East Lothian and Borders Area.

JOSEPH GUY OLLERENSHAW, M.B., Ch.B. General Practitioner, Skipton, Yorkshire.

ROBERT PAUL, M.B.E., M.D., F.R.F.P.S. Lately Director, Pneumoconiosis Medical and Research Bureau, Northern Rhodesia.

ERNEST SCOTT, D.S.O., T.D., D.M. General Practitioner, Ashford, Kent.

FRANCIS EDGAR STOCK, M.B., B.S., F.R.C.S., F.A.C.S., D.T.M.&H. Dean of the Faculty of Medicine, Hong Kong University.

ALFRED VAUGHAN WELLS, M.B., Ch.B., D.P.H., D.T.M.&H. Senior Medical Officer, St. Lucia.

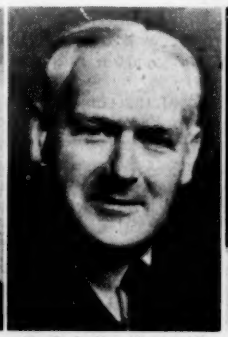
M.B.E. (Military Division)

ALBERT ROSS BOWTELL, T.D., B.M., B.Ch. Major, R.A.M.C., T.A.

GRAEME KERR MATTHEW, M.B., B.Chir. Captain, R.A.M.C.

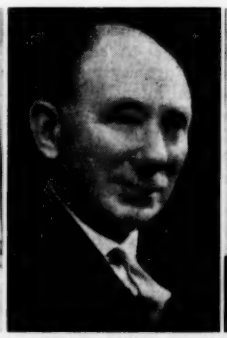
ALAN SWAINSON TOWNSEND, M.B., B.S., D.Obst.R.C.O.G. Flight Lieutenant, Royal Air Force Reserve of Officers (N.S. List).

Dr. H. Guy Dain.

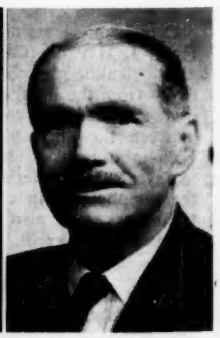


Prof. A. Bradford Hill.

Prof. C. F. W. Illingworth.



Dr. C. G. Magee.



Dr. J. C. R. Buchanan.

M.B.E. (Civil Division)

ERIC VERE CORRY, M.B., B.S. A medical practitioner of Binnaway, New South Wales, Australia.

EILEEN SPENCER MORRIS, M.D. Formerly Medical Superintendent, St. Stephen's Hospital, Delhi, India.

MARGARET ANGUS PATTERSON, M.B., Ch.B., F.R.C.S.Ed. In charge of the Planters' Hospital, Darjeeling, India.

FANNY READING, M.B., B.S. For social welfare services in the State of New South Wales, Australia.

LEONARD ERNEST STEIGENBERGER SHARP, M.B., B.Chir. For public services in Uganda.

The photograph of Professor A. Bradford Hill is reproduced by courtesy of the Wellcome Historical Medical Museum. The photograph of Dr. C. G. Magee was supplied by Bassano, and that of Dr. H. Guy Dain by H J. Whitlock, Birmingham.

IMMUNITY TO PROTOZOA

[FROM A SPECIAL CORRESPONDENT]

A symposium on "Immunity to Protozoa" was held during the spring meeting of the British Society for Immunology at the Middlesex Hospital Medical School on June 1 and 2. At the first session, speakers discussed the general principles of immunity to protozoa: subsequently papers were presented illustrating these principles by reference to specific protozoal infections of the blood, internal organs, skin, and mucous membranes. The proceedings are to be published in book form.

Natural Immunity

Professor P. C. C. GARNHAM (London School of Hygiene and Tropical Medicine), who opened the symposium, confined himself to a few aspects of natural immunity, a subject which he considered offered greater prospects for research than any other at the moment. He referred particularly to the varying degrees of innate immunity found in connexion with the different stages of the life cycle of the malarial parasite. In the natural host all stages occurred normally. In less susceptible hosts parasites would develop in the liver but only invade the blood with low parasitaemia (*Plasmodium bastianelli* in man). If the host was still less susceptible the liver would support normal forms, but the parasite occurred in the blood only as an occult infection (*P. vivax* in chimpanzees); *P. ovale* and *P. falciparum* developed in the liver of the chimpanzee but not in the blood. Finally, rhesus monkeys were completely insusceptible in both the liver and the blood to *P. vivax* infection. The most delicate indication of susceptibility was the development in the host of gametocytes. Professor Garnham gave examples of how in immune hosts these sexual stages were completely inhibited.

Acquired Immunity

Professor EDMOND SERGENT (Institut Pasteur d'Algérie, Algiers) summarized the concepts of latent infection and premunition. He proposed the term "innate immunity" in preference to "natural immunity" to indicate congenital absence of susceptibility to an infective disease; inasmuch as an immunity conferred by any disease was natural, the latter term was too restrictive. Acquired immunity might take two forms. The first was a true sterilizing immunity which succeeded the acute infection and continued long after clinical and microbiological cure. The second was a non-sterilizing relative immunity, called premunition, which accompanied the infection and disappeared with it. Where both host and parasites survived the acute infection, the host resumed the appearance of good health and the parasites, now very rare, lived in a latent state in the tissues, blood, and body fluids. Such latent infection might persist for a lifetime, as in malaria of animals and piroplasmosis; but even after remaining latent for long periods, organisms might still retain a strong potential virulence. Premunition conferred resistance to superinfection by a parasite of the same species. Such resistance might be complete or only partial, but clinical attacks during it were nearly always less virulent than the primary invasion. Premunition kept the body defences permanently on the alert, but, if latent infection ceased, the host became defenceless against reinfection. Therefore, in areas where diseases such as malaria were endemic care should be taken in treatment not to disinfect the host completely and thus destroy his relative immunity.

Professor A. CORRADETTI (Istituto Superiore di Sanità, Rome) defined "sterile immunity" as immunity persisting in the host's body after the complete destruction in it of the infectious agent. It occurred in *Plasmodium berghei* and *Trypanosoma lewisi* infections in the albino rat. The destruction of *P. berghei* in the body of the host took place within 65 days of the primary attack, as revealed by daily sub-inoculations of blood into non-infected animals and by splenectomy. Resistance to reinfection lasted the rest of the rat's life. The maximum survival time of *P. berghei* when reintroduced into such a host was eight days. As reinoculation after splenectomy was constantly followed by rapid multiplication of the parasites, the "sterile" nature of the immunity was evident. Similar immunity developed in *T. lewisi* infection.

Cellular Damage in Amoebiasis and Malaria

Speaking with special reference to amoebiasis and malaria, Professor B. G. MAEGRAITH (Liverpool School of Tropical Medicine) stressed the importance of the constantly shifting balance between the invasiveness of the parasite and the resistance of the host in determining pathogenicity. Studies with five strains of *Entamoeba histolytica*, all known to be active in animals or man, had shown them to possess a variety of proteolytic enzymes, the principal one falling within the trypsin group, as well as fibrinolytic enzymes and in two strains powerful hyaluronidase. In guinea-pigs with acute intestinal amoebiasis injection of trophozoites into the portal vein did not cause liver abscesses: the latter occurred only in animals with a long-standing bowel infection. It appeared that some preparation was necessary before metastatic amoebiasis could occur.

Research into the mechanisms by which malarial infection produced illness in the host had revealed impairment of respiratory activity in liver mitochondria. In the plasma or serum of malaria-infected patients and animals a soluble agent was found which produced similar effects, reducing the respiratory activity of body cells. This discovery prompted reconsideration of the older concept of the liberation of a toxic substance in malaria. Referring to these studies in his final remarks, Professor W. H. TALIAFERRO (Argonne National Laboratory, U.S.A.) stated that pathogenicity was central to the theme of immunity to protozoa: it varied inversely with immunity and might be defined as a combination of invasiveness and toxogenicity.

Genetic and Congenital Immunity

Dr. A. C. ALLISON (National Institute for Medical Research, London) reviewed evidence that inherited factors in blood conferred resistance to malaria. Young children with the sickle-cell trait or with sex-linked deficiency of erythrocytic glucose-6-phosphate dehydrogenase were protected against falciparum malaria. Thalassaemia and haemoglobin E probably also gave some protection. Because of this advantage the corresponding genes could become common in malarious regions. Acquired immunity in older children reinforced this natural immunity and in adults overshadowed it.

Surveying the subject of congenital immunity in malaria, Dr. L. J. BRUCE-CHWATT (W.H.O., Geneva) said there was much indirect parasitological and epidemiological evidence that in areas of high endemicity, where the population showed an enhanced tolerance to malaria, passive transfer

of immunity from the mother to the newborn played a part in protecting the infant during its early phase of life. Most of this immunity was transmitted before birth, probably through the placenta. With rodent malaria it had been shown that in mice and rats the congenital immunity was transmitted after birth mainly through the milk of immune mothers, though some pre-natal transfer of protective antibodies also occurred. Investigations on simian malaria might elucidate many obscure points so far as the congenital immunity of primates was concerned. The stage of relative insusceptibility of very young infants born to mothers with a degree of tolerance of the malaria parasites was transient and preceded the next stage in the host-parasite relationship which represented the trough of the immunological wave. During that period the morbidity and mortality of infants and children in tropical Africa was at its peak; it decreased as the acquired immunity began to protect the semi-immune African child from about the age of 5 years onwards.

Gamma Globulin in Human Malaria

Dr. S. COHEN (Wright-Fleming Institute, St. Mary's Hospital, London) showed in studies with Dr. I. McGREGOR in the Gambia that acquired immunity in human malaria was fundamentally dependent upon the production of circulating antibody which is associated with the 7-S gamma-globulin fraction of the serum. The gamma globulin was prepared by chromatography from pooled sera of apparently immune adults. When injected into Gambian children suffering from acute *P. falciparum* malaria with dense parasitaemia, the gamma globulin reduced trophozoite counts to negligible numbers within four days and alleviated clinical signs of illness. The dose of immune gamma globulin, which was administered by intramuscular injection, was equivalent to about 10% of the recipient's own gamma globulin and did not maintain protection for longer than three months. Other fractions of adult Gambian serum, including 19-S gamma globulin, had no protective effect, neither did gamma globulin prepared from healthy U.K. blood donors. The maintenance of malarial immunity in a hyper-endemic area was associated with a very considerable increase in the rate of gamma-globulin production. Thus, adult Gambians were shown to produce about eight times more gamma globulin per day than healthy U.K. adults, although rates of albumin synthesis were the same in both. The protection of adults by chemoprophylaxis for three to five years reduced the rate of gamma-globulin synthesis by 3–4 g. per day, which was more than the total amount synthesized by healthy Europeans. The malarial parasite constituted a very complex antigenic stimulus, and probably only a small proportion of the gamma globulin produced in response to malarial infection was, in fact, specific protective antibody.

Anaemia in Malaria

Dr. A. ZUCKERMAN (Hadassah Medical School, Jerusalem) observed that anaemia in malaria occurred only at or after crises and that more erythrocytes were destroyed than could be accounted for by rupture of parasitized cells. Erythrophagocytosis in malaria affected apparently normal as well as parasitized erythrocytes: this occurred in man and in other plasmodial infections in monkeys, rats, and chickens. In her experiments the Coombs test for antiglobulin was negative until the crises, but thereafter remained positive until parasites disappeared from the blood. She suggested that parasitized cells might become sufficiently altered to become auto-antigenic and that this might explain the erythrophagocytosis after malarial crisis.

Antibody Response to Trypanosomes

Professor W. H. TALIAFERRO discussed cellular and humoral aspects of immunity in protozoal infections, and reported his work on ablastic immunity to *Trypanosoma lewisi* infection in rats. For the first few days trypanosomes divided rapidly; subsequently they persisted in the blood without evidence of nuclear division. This inhibition of reproduction was associated with the production by the host of ablastin, which was considered to be an antibody. As ablastin appeared in the blood the glucose metabolism of the parasite altered, nucleic-acid synthesis was completely inhibited, and protein synthesis diminished. Similar effects followed the passive transference of ablastin. In *T. lewisi* infection three sets of antibodies were produced: the first inhibited reproduction, the second effected partial cure of the infection, and the third was lytic in character and was highly curative against second infections. Professor Taliaferro mentioned the different avidity of antibody components in sera. He considered that normal antibodies of low titre in the presence of constantly forming complement were more effective than high-titre antibodies.

Dr. W. E. ORMEROD (London School of Hygiene and Tropical Medicine) did not consider the transition from the predominance of variable young forms to uniform adult forms in *T. lewisi* infection necessarily indicated the action of a factor—ablastin—inhibiting reproduction. He thought the phenomenon could be partly explained by the selective killing of growing forms with sparing of the adults.

Mr. K. N. BROWN (National Institute for Medical Research) spoke of the remarkable ability of trypanosomes to change their antigenic character in response to the immune reactions of the host. No sooner did the host clear its blood of parasites by the production of a specific lysin than the trypanosomes began to appear in another antigenic form. This interplay of antigenic variant and specific antibody formation largely explained the chronic nature of sleeping sickness, particularly the *T. gambiense* form.

Immunity to Toxoplasmosis

Professor C. P. BEATTIE (University of Sheffield) discussed immunity to *Toxoplasma*, a parasite which was versatile, well adapted, and widespread in man and animals throughout the world. Occasionally it produced serious illness, but for the most part it did little harm.

Toxoplasmata isolated from latent infections were of low virulence. This might be the most important factor. Antibodies were readily formed in response to infection, but, by themselves, had little effect in preventing or curing illness. They might, while contributing to resistance, also indicate the development of cellular defence. An attractive theory was that resistance was due to latent infection—premunition. In favour of this was the observation that recovered animals resisted subsequent infection unless with a massive dose of a highly virulent strain. Infection had been shown to persist in animals and man for a long time. In many respects infection with *Toxoplasma* resembled infection with the tubercle bacillus. Both were followed by lifelong allergy. As with tuberculosis, vaccination with killed organisms failed to produce good protection. The inoculation of a live attenuated strain was, however, effective, and might be of value in animals, particularly sheep, in which species *Toxoplasma* appeared to be one cause of abortion.

Dr. J. D. FULTON (National Institute for Medical Research, London) spoke on serological tests in toxoplasmosis. The occurrence of antibodies to *Toxoplasma* in the serum of man and animals was widespread throughout the world, and a profusion of tests for their detection had been described, including complement-fixation, skin-neutralization, and sensitivity tests and a dye test. More recently, other tests had been developed based on haemagglutination, fluorescence-inhibition, precipitin, direct agglutination, and flocculation reactions, as well as a respiratory-inhibition test using a pure preparation of parasites. Dr. Fulton briefly evaluated the various tests and emphasized the need for international standardization. In this country two toxoplasmosis reference laboratories had been established.

Leishmaniasis

Professor S. ADLER (Hadassah Medical School, Jerusalem) spoke of immune phenomena in leishmaniasis, with particular reference to Oriental sore. Strains of *Leishmania tropica* retained infectivity for man indefinitely. Following intradermal injection of *L. tropica* a proliferation of histiocytes occurred which, however, had no effect against the multiplication of the parasites. Then the lesion was invaded by round cells, lymphocytes, and plasma cells; the histiocytes disappeared and so did the leishmania. After spontaneous cure there was persistent immunity in almost all cases. No immunity developed in man until he had gone through the whole gamut of changes that led to spontaneous cure. Surgical removal of the lesion might permit reinfection. In South American cutaneous leishmaniasis histological changes were similar to those caused by *L. tropica*, and solid immunity was conferred. In espundia there was, in many cases, a local lesion as in Oriental sore. Within a variable time of spontaneous healing metastatic lesions developed in the nose and mucocutaneous surfaces and the skin. Histologically, these lesions contained very few parasites, but histiocytes were very numerous and lymphocytes and plasma cells were also present. The Montenegro test—using leishmanin—was non-specific within the leishmanial group, but was the chief aid to diagnosis in espundia.

Prevention of Kala Azar

A communication was received from Dr. P. E. C. MANSON-BAHR (Nairobi) describing experiments in active immunization in leishmaniasis. Inoculation intradermally and subcutaneously of a human strain of *Leishmania donovani* caused a small leishmanial skin lesion, which was followed four to six months later by visceral spread and the production of the kala azar syndrome. The isolation by Heisch from rodents in Kenya of strains of leishmania which were dermatropic, since they caused dermal and not visceral lesions when inoculated into man, suggested a means of active immunization in kala azar. Experiments with volunteers had confirmed that inoculation of a live leptomonad culture of leishmania, isolated from a ground squirrel, caused the intradermal leishmanin test to become positive in six to eight weeks and conferred protection against a live culture of *L. donovani*. It remained to be demonstrated if vaccination with the ground squirrel strain would protect against infection acquired naturally and that the strain was completely safe and would not cause kala azar.

HOSPITALS OF THE FUTURE

The planning of the hospitals of the future was discussed by Mr. GORDON A. FRIESEN, a hospital planning consultant from Washington, D.C., at a meeting arranged by King Edward's Hospital Fund for London at St. Bartholomew's Hospital on June 2. Mr. Friesen is the national consultant to the Surgeon-General of the American Air Force and a university lecturer on hospital administration. Lord CUNLIFFE was in the chair.

More Care in Design

Mr. FRIESEN illustrated his lecture with slides of various hospitals in America and Canada and diagrams of hospital plans. He emphasized that the problem was the same in all countries, adding, "We are all interested in the same basic philosophy, and that is to take care of the whole patient—the mental, physical, and spiritual aspect of the patient. There is a tendency in the hospital world, when discussing planning, to say that because we are thinking of the patient we are different. That is nonsense. If we are interested in the care of the patient, we should take a little more care in the design of the hospital which we are building. It does not matter whether it is round, square, or rectangular. The essential point is *not* to build the building first and then adjust the organization to suit the building. Let us first of all develop the organization and then put a roof over it, as industry does."

Because of the high operating costs, it was important to use new methods. In most hospitals 50% of the nurse's time was spent in collecting supplies, running backwards and forwards. "Even a bricklayer has a hod and does not collect one brick at a time," Mr. Friesen said. "Isn't a nurse as important as a bricklayer?" He gave the illustration of a sheet which was handled 16 times between leaving the ironing-board and reaching the bedside, being transferred time and again from one cart to another on its way to the ward. "We spend more money on worrying about accounting for the sheet," he said, "than it would cost to replace the sheet if it were lost." He also complained of the practice of washing everything by hand in every department; there should be a central washing area, to which everything was sent by conveyor system and washed mechanically. Linen should be similarly handled, with a clearcut division between dirty and clean linen.

Centralization

Centralization was the theme, too, of the feeding arrangements, for he spoke of a hospital which could provide 225 trays of food an hour from the central kitchen, each tray taking no more than three minutes to reach the bedside. He described a cafeteria planned to avoid queueing; by a circular plan it was possible for anyone to go to any point of food supply. Mr. Friesen also stressed the importance of having equipment and hospital furniture designed for its purpose; it was wrong simply to take what the manufacturers put on the market. As far as possible furniture should be interchangeable and easily movable. Hospitals should provide facilities for next-of-kin to be with patients. "If a husband can hold his wife's hand, it does more good than a lot of medicine."

In the discussion, Miss M. M. PUDDICOMBE (matron of Addenbrooke's Hospital, Cambridge) said nurses would acknowledge that Mr. Friesen had accurately high-lighted the pantomime which they had enacted for years. They would welcome automation if their tired feet and aching backs were eased, and the wear and tear were taken by machinery. But could this centralization be introduced in the smaller hospitals? Mr. FRIESEN said he saw no reason why there should be any difference in smaller hospitals. He was building a 50-bed unit near Washington with the same centralized system. Mr. S. HODKINSON (Wolverhampton Hospital Management Committee) asked whether there was a limit to the size of a single kitchen in a large hospital. Mr. FRIESEN replied that in a 2,500-bed hospital in Vienna there was only one kitchen, and he did not think there should be more than one. If it were properly designed it did not matter how large the hospital was.

The Ophthalmic Optician and the Dispensing Optician is a revised edition of the booklet in the Choice of Careers series published by the Central Youth Employment Executive. It opens with a brief summary of the development of the profession from the fourteenth century (and the peddling of spectacles at fairs and from door-to-door) to modern methods of testing vision and correcting defects. There are chapters on the day-to-day work of an optician and on the qualities and skill which the work demands. Details are given of the educational qualifications required and of the professional examinations, training courses, and openings and salaries of qualified opticians. (H.M.S.O., No. 74, price 6d. net.)

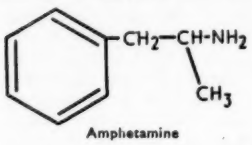
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

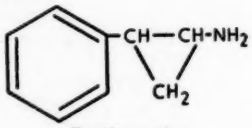
Tranylcypromine

"Parnate" (Smith Kline and French).

Chemistry.—This drug, which is trans-(±)-2-phenylcyclopropylamine sulphate, is closely related to amphetamine, as the following structural formulae show:



Amphetamine



Tranylcypromine

Pharmacology.—Tranylcypromine stimulates the central nervous system. It is a monoamine oxidase inhibitor, but unlike iproniazid and its analogues it is not a hydrazine. It seems unlikely that all the pharmacological effects of these drugs are related to inhibition of monoamine oxidase; other enzyme systems also appear to be involved.

Therapy.—Like other monoamine oxidase inhibitors, tranylcypromine is useful in mild depressive states, particularly those accompanied by symptoms of anxiety or feelings of fatigue. It should not be given alone for severe depression: E.C.T. is still necessary for many cases of endogenous, and certainly all of severe, depression. Given in conjunction with E.C.T., tranylcypromine may reduce the number of shocks needed and prevent subsequent relapses, but in general imipramine is a more effective drug in such cases. Depression occurring in schizophrenia controlled by phenothiazines may respond to tranylcypromine; careful supervision is essential because of the danger of causing the schizophrenia to flare up. Tranylcypromine may act within 24–48 hours, which is quicker than other monoamine oxidase inhibitors, such as phenelzine ("nardil") and isocarboxazide ("marplan"); but there is no evidence that parnate is otherwise superior clinically.

A dose of 10 mg. (1 tablet) b.d. should produce a response within a week. If there is no response, the dose may be increased to 10 mg. t.d.s. for a further week, and then to 20 mg. b.d. There is rarely any therapeutic advantage in giving more than this, and side-effects become increasingly prominent. The time for which the drug must be continued varies from patient to patient, and a suitable maintenance dose for each patient should be found by trial and error.

Side-effects.—These are similar to those of other monoamine oxidase inhibitors. The most common are: feeling of faintness, sleepiness or decreased need for sleep, dry mouth, constipation, excessive flatus, sexual difficulties, headache, rashes, restlessness, neuromuscular and sensory disturbances, and oedema. Mania has not been reported, but is a possibility when high doses are given. Most of these complications can be relieved by reducing the dosage. Oedema responds to diuretics.

N.H.S. Basic Price.—100 tabs., 35s. 6d.

An account has now been printed of the First All-Asian Congress of Paediatrics, which was held in New Delhi, India, from January 2 to 6 this year. It includes the address of the President of the Congress, Dr. K. C. CHAUDHURI, and synopses of papers given under the sectional headings of cardiology; diseases of the gastro-intestinal system; haematology; infectious diseases; the nose; miscellaneous; diseases of the nervous system; nutritional disorders and infant feeding; social paediatrics; surgery; and tuberculosis. The congress was sponsored by the Indian Paediatric Society and the Association of Paediatricians of India.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Research on Prescribing Habits

SIR,—A number of serious and urgent health problems are arising in connexion with the current revolution in our use of drugs. This revolution would appear to be far from bloodless, and we are obviously in grave danger of doing more harm than we might suspect. For this reason, we consider that your suggestion (May 27, p. 1520) for a register of drugs capable of producing blood dyscrasia is timely, and we feel that the existing machinery for the notification of disease might well be employed. If these blood dyscrasias were made notifiable, it is probable that the clinical picture is spectacular enough for a high proportion of them to be reported.

From a rather cursory study of the disposal of E.C.10's in this area, we are inclined to believe it possible to intercept prescriptions which had been dispensed to the patient concerned during the months preceding notification, and in this way establish an association between disease and drug.

Furthermore, your leading article on drug-induced blood dyscrasia should make us think yet again about *all* the unpleasant side-effects of our new treatments. That they are not confined to organic damage alone is shown by the Brain Report,[1] with its emphasis upon drug dependence and minor addiction. While more pharmacological research is obviously needed, we would also like to see studies of every aspect of our national prescribing habits, so that a more rational social policy governing the purchase, distribution, prescription, and evaluation of drugs may be developed.—We are, etc.,

JAMES CROOKS.
E. MAURICE BACKETT.
University of Aberdeen.

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[1] *Drug Addiction: Report of the Interdepartmental Committee*, 1961. H.M.S.O., London

Connective Tissue

SIR,—In his letter (May 20, p. 1459) Dr. C. H. Lack suggested that degradation of periendothelial matrix by plasmin may be the basis of certain disorders of connective tissue. As an alternative to "auto-immune" hypotheses, his concept of a primarily "autolytic" pathogenesis is favoured by evidence emerging from several lines of investigation.

Capillary resistance, measured by negative-pressure tests, was frequently found to be subnormal in patients with rheumatoid arthritis. This abnormality could result from a structural weakness of connective tissue ensheathing small cutaneous blood-vessels.[1] In many individuals the level of capillary resistance showed rapid fluctuations, indicative perhaps of changes occurring primarily in the amorphous ground substance rather than in the relatively inert fibrillary components of the sheath.[2] Thus the low level of capillary resistance in rheumatoid arthritis might well reflect the occurrence in periendothelial matrix of the enzymatic damage envisaged by Dr. Lack. The collapse of rabbits' ears following intravenous papain, first reported by Thomas in 1956,[3] is a closely analogous experimental situation, where loss of rigidity in cartilage is the clinical sign of

reversible enzymatic damage to the amorphous component of matrix. Dr. Lack mentioned that cortisone delayed restoration of the matrix following chondrolysis. McCluskey and Thomas[4] have reported a similar action of cortisone, hydrocortisone, and prednisolone upon the cartilage of papain-treated rabbits.

At least one of the serological features of rheumatoid arthritis may have an enzymatic basis. The "antinuclear factor" found in the serum of the majority of patients[5] appears to be a basic protein closely related to or identical with an enzyme or family of enzymes with bacteriolytic activity.[6] Concerning Dr. Lack's concept of a release of plasminogen due to increased vascular permeability, it is relevant that lysozyme present in normal serum has no "antinuclear" activity, and, from the analogous behaviour of papain protease, it can be inferred that lysozyme is normally bound to other proteins in serum. It was concluded that the effects of intravenous papain on cartilage in rabbits were produced by molecules of enzyme which remained—briefly—in an unbound, readily diffusible state after entering the circulation. The remaining molecules were bound by alpha-2-globulin, presumably forming a complex molecule sufficiently large to be incapable of entering cartilage.[7] Similarly, a positive test for "antinuclear factor" in rheumatoid arthritis may reflect inadequate binding of lysozyme in serum, and signify the presence of free enzyme capable of passing from the circulation and into tissues. It is likely that potentially harmful enzymes do enter the circulation in the course of tissue breakdown due to injury or infection. Any tendency for these enzymes to act upon susceptible substrates in healthy tissue may normally be obviated by binding mechanisms capable of retaining enzymes within the circulation.

We would agree with Dr. Lack's suggestion that autoimmunity could be a consequence rather than the cause of disorders of connective tissue; the possibility that immune responses might also maintain systemic disease initiated by enzymatic damage has been considered.[8] The hypothetical role of the reticulo-endothelial system could be the development of cell-borne or humoral hypersensitivity to antigens created by enzymatic degradation of components of tissue. In this way the immune response would be qualitatively similar to that occurring under the stimulus of other foreign proteins; the concept of hypersensitivity to truly *native* components—that is "auto-immunity"—may be irrelevant. Finally, Dr. Lack's ideas and those outlined above have evolved on the basis of independent clinical and experimental studies. Though differing in detail, they have in common the concept that some abnormality of the distribution and fate of enzymes *in vivo* may be of fundamental importance in the development of the disorders of connective tissue.—We are, etc.,

J. L. POTTER.
J. J. R. DUTHIE.

Rheumatic Diseases Unit,
Northern General Hospital,
Edinburgh 5.

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SIR,—May I support the remarks of Dr. C. H. Lack (May 20, p. 1459) on the role of the ground substance in connective-tissue disease? We have been studying this for some time, and have found that agents which preclude polymerization of mucopolysaccharide prevent collagen-deposition in newly formed granulation tissue of healing. The agent we have used principally has been testicular hyaluronidase, which contains a hyalase and sulphatase. This has no inhibiting effect on the contraction of a superficial wound. This process is brought about by cellular activity. (Contraction also takes place in scurvy, where again collagen is not formed.) We are now endeavouring to determine which of the mucopolysaccharides are important.

We have also been interested to study the significance of blood factors, such as plasmin. We are currently studying the effect of the polypeptide bradykinin. Although this appears to produce an early and increased exudation in a wound, we have not found any increase in collagen formation when the drug is locally exhibited repeatedly. (We are very much indebted to Dr. Holgate, Research Director of Sandos Ltd., for our supplies of this drug.)

It is our conviction that although collagen-formation may be a useful or important and obvious change in the process of wound-healing and in connective-tissue disease, it is not the most significant change, but is a by-product of inflammatory processes. Like Dr. Lack, we feel that the term "collagen disease" is a poor one. It describes a biochemical symptom, but is of no more value in classification than the "fever" of the ancient physicians.—I am, etc.,

GEORGE T. WATTS.

Division of Wound Healing Research,
Department of Surgery,
University of Birmingham.

Evolution of the Mental Hospital

SIR,—I should like to congratulate Dr. A. B. Cooper and Dr. D. F. Early on their article, "Evolution in the Mental Hospital" (June 3, p. 1600). I wish particularly to endorse their view that the mental hospital must not become a hostel or a geriatric or a chronic-sick unit.

In my view the modern hospital, probably in the future, associated with its own psychiatric unit in a near-by general hospital, is an active treatment hospital first and foremost. It is there primarily to treat and cure the mentally ill. Its discharge rate should nearly equal its admission rate. It will, of course, have to care for a small number of long-term incurable cases, but these cases must primarily be psychiatric cases which require the support and skill of the psychiatrist and psychiatric nurse and not just elderly or infirm people.

Dr. Early has ably demonstrated that probably 30% of our long-stay patients do not require psychiatric care. It is therefore most essential that local authorities, in close co-operation with mental hospitals, provide hostels, but, above all, that the geriatric service, both chronic sick and Part III, realize that they must provide the necessary accommodation for many patients who would not be remaining under psychiatric care.

The psychiatrist and the psychiatric nurse must not be wasted looking after the elderly—they must be freed for the treating of the neurotic and psychotic. Facilities for the proper and time-consuming work of treating neurosis, which includes character disorders and psychopathy, are still sadly lacking. It may well be that parts of mental hospitals in the future could be used for the care of the elderly and infirm, but the medical and

nursing staff must be provided by the geriatric services rather than the psychiatric, as is so often the case at present.—I am, etc.,

The Towers Hospital, Humberstone, Leicester. H. B. KIDD.

Simulated Toxic Psychoses

SIR,—It is common knowledge that chlorpromazine causes jaundice in about 2% of cases treated; it is also well known that this drug may cause eosinophilia and occasionally agranulocytosis, and also certain physical and mental symptoms. It is less widely known that it will cause changes in the E.S.R., in the total and differential white cell count, and in liver function tests (even in patients without clinical jaundice). It is still more rarely appreciated that such changes, together with drowsiness, occasional rise of temperature, intestinal disturbances, flaring up of arthritis, etc., may be due to this drug, unless one knows that it has been given in the recent past—the changes may persist for 1–3 weeks after its withdrawal; and yet this situation occurs fairly often.

During the past few years quite a number of admissions to this and other mental hospitals have shown clinical, and more often laboratory, findings which have roused the suspicion of a toxic-infective psychosis. Repeated physical examinations, often by several specialists, have failed to reveal any illness that would account for the increase in total white cell count (up to 15,000 per c.mm. and more, often without left shift) or its decrease (to less than 3,000 per c.mm.); for the increase of eosinophils and monocytes (to 10% and more), of the E.S.R. (often to more than 20 mm./first hour), and sometimes of transaminase levels; for a raised thymol reaction (often 2–4 units, occasionally more, with flocculation), or for the clinical findings described above. These changes might all occur together, or, more often, only some might be present. We were rather puzzled by these happenings, until it occurred to us that both the clinical and the laboratory disturbances might be due to drugs administered before admission. In several such cases thorough inquiry revealed that the patients had been having chlorpromazine but that it had not been reported on admission. Comparison of our findings in cases known to be having chlorpromazine with the "inferred" ones showed the changes to be similar.

It appears therefore most desirable that, when patients are sent for admission to a mental hospital, their doctor should state whether they are having phenothiazine treatment (particularly chlorpromazine) or amino-oxidase inhibitors. The effects of these drugs may not only simulate toxic-infectious psychoses, but may also mask true physical illness, as we have not infrequently seen in this hospital.—I am, etc.,

Department of Pathology, Shenley Hospital, Near St. Albans, Herts. H. H. FLEISCHHACKER.

Peak Expiratory Flow Rates

SIR,—Those who are attempting to assess the limits of normal ventilatory function at pre-entry examination of recruits to industry will be grateful to Dr. C. M. Tinker for giving some guidance in her recent article (May 13, p. 1365) on the peak expiratory flow rates as measured with the Wright peak flowmeter.

I have recently reviewed the results obtained during the last few months at the examinations of over 400 recruits to a heavy manual industry in the north-east ports. I have attempted to classify these into ten grades. All the subjects were under the age of 40 and the majority were in the 20–29 year age-group. None of these subjects were rejected for detectable chest disease and they were all within the acceptable physical standards for entry into the industry. The classification of the results was as follows:

	Peak Flow Rate	*Number of subjects*
Grade 1.	Under 300 litres/min.	2
Grade 2.	300–349 ,,	7
Grade 3.	350–399 ,,	10
Grade 4	400–449 ,,	49
Grade 5.	450–499 ,,	97
Grade 6.	500–549 ,,	115
Grade 7.	550–599 ,,	68
Grade 8.	600–649 ,,	57
Grade 9.	650–699 ,,	11
Grade 10.	700 litres/min. and over	5
	Total	421

It will be noticed that 50% of the subjects in this group fall into grades 5 and 6, and only 29% are in grades 7 and 8.

The formula given by Dr. Tinker for estimating the peak flow rates of normal men at any age—e.g., 770 – 4½ × age—would suggest that in the age-group 20–39 years the majority should fall in the range between 595 and 680 litres/min. This would correspond with grades 8 and 9 on my scale except for a few of the oldest men, in the 38–39 age group. Dr. Tinker states, "It must be remembered, however, that values as much as 200 l./min. greater or less than this figure are within normal limits." If this is so all subjects below the age of 40 with peak expiratory flow above 395 can be judged to be within normal limits. In my series of recordings there were 19 subjects with a peak expiratory flow below 399 (all were below 395) and fell into grades 1, 2, and 3. All should be considered as having abnormally low ratings on the Tinker formula, and one is left asking oneself, "What is the significance? Should these men be rejected as bad risks?"

Experience in the use of the Wright peak flowmeter makes me wonder exactly what value the use of this instrument has for estimating whether a subject is within normal limits and has sound lung function. In practice it has been found that so many factors obviously affect recordings that it is little wonder that wide variations from the expected rates are found. Conditions of the lip and mouth, which may be easily overlooked, clearly affect the rates in some cases, and the possession of a partial or complete denture, labial fissures and herpes labialis, sore tongue, and sore throat are among some of the conditions already met with. Upper respiratory infection, allergic rhinitis, and nasal obstruction have accounted for other low readings. Conditions of the chest cage, and even tight strapping of the ribs, can diminish the peak expiratory flow. It is most important to realize that the normal degrees of chest movement are influenced by such things as posture, load carrying, and strenuous manual activity and that these influence the peak expiratory flow. Finally, the degree of co-operation of the subject can be most variable, so that it is necessary to allow more than the recommended number of trial blows in those with low intelligence or who are clearly apprehensive about the procedure.

Quite clearly more study and experience in the use of this apparatus are required before full judgment can be passed upon its final place in the diagnostic

armamentarium. One had hoped that it might approach the sphygmomanometer in general usefulness, but so far it has been difficult to decide where normality ends and abnormality begins in supposedly healthy subjects.—I am, etc.,

Beverley, East Yorkshire. JOHN M. JACKSON.

Unrelieved Distress in Asthmatic

SIR,—I wish to record what to me was an unusual occurrence in the treatment of bronchial asthma—that is, a clinical response to aminophylline unaccompanied by relief of distress.

The patient was a male in his early forties, of thin build and well known to have bouts of bronchial asthma. He had been hospitalized for asthma a few months before. The present illness began with three afternoon attacks which were relieved by parenteral aminophylline. The next morning the patient began the day with such breathlessness that he stayed in bed. He was given two ampoules of intramuscular "cardophylin" (aminophylline) at that time (which had worked on the three preceding days). This gave unsatisfactory relief and I was called to the house at tea-time. I gave two ampoules of intravenous cardophylin. At about 1¼ ampoules the patient's respiration changed from a shallow, wheezy, 30 per minute, of inadequate volume, to about 20 per minute with no wheezing and of a tidal volume clinically much greater than normal. I was rather surprised that, despite the achievement of an adequate respiratory exchange, the patient's distress did not disappear or improve.

The patient was at no time cyanosed, and I regret that, in the absence of a respirometer and suitable bottles for blood CO_2 and O_2 concentrations, I could not get the information that I would have preferred to have. Under the circumstances, and with the house in a hollow, I decided that hospitalization, where there would be a change of environment and oxygen available, would be the wisest course of action. I would be pleased to hear of any suggested further management for such a patient at home showing a clinical respiratory response to treatment but no alleviation of distress.—I am, etc.,

Hankelow, Cheshire. D. H. BAILEY.

Chagas's Disease

SIR,—We were very interested to read your annotation about Chagas's disease (May 20, p. 1451). This disease is a very important pathogenic problem in our country, Venezuela, as it is in all Latin America.

We would like to emphasize certain facts about the diagnosis of this disease. We agree that in the early stages "xenodiagnosis" is probably the best method, but in the later stages other methods are available, namely: direct examination of the parasite in blood (specially in thick drop), and cultures and direct examination of living tissues such as biopsy of lymph nodes, cutaneous and conjunctival biopsy, and cardiac and hepatic viscerotomy. Indirect methods are also available, one of these, named Machado-Guerreiro test, which is a complement-fixation test, is widely used in Venezuela for diagnosis of the disease.—We are, etc.,

RAFAEL A. BARRETO.
London N.W.6. JESUS VIDAL.

Teats

SIR,—The "feeding-bottle vacuum" problem which is causing concern to Dr. Ian Wickes (June 3, p. 1606) should not, I feel, be a problem at all—particularly to those experienced in the artificial feeding of normal and premature infants. Rather is it a question of technique and without blame to baby, bottle, or teat!

If, during the course of the feed, the teat, while still being kept in the infant's mouth, is gently but firmly drawn over to one side, air will enter through the resulting temporary space in the mouth, bubble back into the bottle, and all will be well. This allows the baby a momentary rest from sucking and does not cause him to release hold on the teat. And in case a further difficulty is raised, it does *not* cause wind. This simple procedure can equally well be used with a pipette, and no extra device therefore to let air in during sucking is needed which would inevitably, as Dr. Wickes allowed, cause milk to escape when the pipette was temporarily laid down.

I have fed babies thus for many years and have never experienced any difficulty in this particular respect.—I am, etc.,

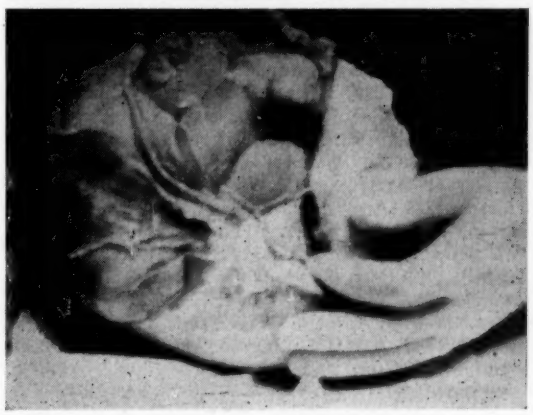
Bassett, Southampton. D. C. SCOTT.

Advanced Ectopic Pregnancy

SIR,—Advanced ectopic pregnancy is a rare, but fascinating, condition that has always attracted interest. It occurs only once in approximately 12,000 pregnancies. Yahia and Montgomery reported 8 cases among 68,400 deliveries.[1] The subject has been discussed by Mahfouz,[2] Ware,[3] de Villiers,[4] King,[5] Charlewood and Culiner,[6] and Chassar Moir.[7] The world literature has been recently reviewed by Poddar.[8]

According to Clark and Bourke[9] the term is used when the pregnancy is over 12 weeks. The following case report is of interest not only because of the rarity of the condition but also because of the pitfall in diagnosis.

Mrs. W. M., aged 30 years, was admitted on May 17, 1957, because of swelling of the abdomen of eight months' duration and of amenorrhoea of 18 months' duration. She had three full-term normal labours resulting in living children, the youngest child being 4 years old. There was no history of abortion. On examination, the general condition was satisfactory, pulse rate 84 per minute, blood pressure 110/70, and the chest and heart normal. Abdominal examination revealed a mobile, cystic swelling, the size of a 32-weeks pregnancy. The girth of the abdomen at the level of the umbilicus was 30 inches (76 cm.). On



pelvic examination the cervix was long and firm, but the body of the uterus could not be felt separate from the mass. The condition was diagnosed as ovarian cyst. A plain *x*-ray of the abdomen was advised but was not done owing to technical difficulties.

The following investigations were carried out: Urine normal; blood picture, haemoglobin 75%, red cells 3,750,000/c.mm., white cells 6,850/c.mm.; erythrocyte sedimentation rate 8 mm./per hour; Kahn flocculation test negative.

Laparotomy was carried out and a huge cyst, apparently seated on the uterus, which was small and pushed to the right, was found. Small fine adhesions yielded to finger dissection; the lower part of the cyst was tied off and the cyst easily removed. Its surface was smooth and it had a thick wall. Only when it was opened was the condition recognized as a foetal sac of an advanced extrauterine pregnancy (see Fig.). The post-operative period was smooth and the patient left the hospital after 17 days.

The diagnosis of advanced extrauterine pregnancy is often difficult and this often leads to delay which in turn increases the risk, at least to the foetus. King[5] pointed out that the diagnosis is often missed simply because this rare condition is not considered. The most important attribute leading to successful diagnosis is to develop the "high index of suspicion" advocated by Cross *et al.*[10]—I am, etc.,

Mecca Maternity Hospital, Saudi Arabia. A. A. HAMMOUDA.

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Medical V.C.s

SIR,—I have recently been engaged in studying the records of medical men who have been awarded the Victoria Cross, and it occurs to me that it might be of interest to your readers to have some information of the various medical schools and universities at which the recipients received their training. Thirty-seven doctors have received this coveted decoration since it was established by the Royal Warrant of January 29, 1856; two of these received a clasp for a second act of gallantry. The various hospitals and universities are as follows:

England (16).

University College: Mouat, 1854 (6th Dragoons); Martin-Leake, 1902 (South African Constabulary), clasp, 1914 (R.A.M.C.); Inkson, 1900 (R.A.M.C.). *Guy's:* Maillard, 1898 (Royal Navy); Ackroyd, 1917 (R.A.M.C.). *St. Thomas's:* Manley, 1864 (Royal Artillery); Maling, 1915 (R.A.M.C.). *King's:* Le Quesne, 1889 (Army Medical Staff). *St. Bartholomew's:* Green, 1916 (R.A.M.C.); Whitchurch, 1895 (I.M.S.). *Middlesex:* Fox Russell, 1917 (R.A.M.C.). *London:* Howse, 1900 (New South Wales Medical Staff Corps). *Manchester:* Nickerson, 1900 (R.A.M.C.). *Sheffield:* Allen, 1916 (R.A.M.C.). *Liverpool:* Chavasse, 1916, clasp, 1917 (R.A.M.C.). *Oxford:* Maling and Chavasse. *Cambridge:* Green and Ackroyd.

Scotland (9).

Edinburgh: Sylvester, 1855 (23rd Foot); Jee, 1857 (78th Foot); G. M. Douglas, 1867 (24th Foot); McCrea, 1881 (Cape Mounted Yeomanry); McMaster, 1857 (78th Foot). *St. Andrew's:* Hale, 1855 (Royal Fusiliers); Home, 1857 (90th Foot). *Glasgow:* Babtie, 1899 (R.A.M.C.); Ranken, 1914 (R.A.M.C.).

Ireland (8).

Bradshaw, 1857 (90th Foot). *Dublin:* Crimmin, 1889 (Bombay Medical Service); Reade, 1857 (61st Foot); Temple (Trinity College, Dublin), 1863 (Royal Artillery); Reynolds (Trinity College, Dublin), 1879 (Army Medical Department); Crean (R.C.S.), 1901 (Imperial Light Horse). *Cork:* Lloyd, 1893 (Army Medical Staff). *Belfast:* Sinton, 1916 (I.M.S.).

Canada (2).

Ontario: H. E. M. Douglas, 1899 (R.A.M.C.). *McGill:* Scrimger, 1915 (Canadian Army Medical Service).

United States (1).

N.W. University, Chicago: Hutcheson, 1918 (Canadian Army Medical Service)

Allen, Chavasse, Green, and Russell won their crosses as Territorials.

It will be noted that some details are missing and possibly some of your readers will be able to fill the gaps. A case of special interest is that of Henry John Andrews who won a posthumous cross at Waziristan in 1919 as a captain in the I.M.S. He served in the Salvation Army for thirty years. He was largely instrumental in starting the medical side of that organization in India, beginning with a small medicine chest and a razor and penknife as his surgical armamentarium. He did such excellent work that his leaders assisted in sending him home to get qualified; we have no information as to which medical school he attended and from which he qualified with honours.—I am, etc.,

R.A.M.C. Historical Museum, Queen Elizabeth Barracks, Crookham, Hants. R. E. BARNSLEY.

Safety Belts in Cars

SIR,—If both front-seat passengers in all cars wore safety belts I think there would undoubtedly be a reduction in the severity and probably in the number of the injuries with which we are all too familiar. An increase in the number of whiplash injuries of the neck, however, is quite likely, and with the body being held more rigidly an increase in the incidence of severe cervical cord damage may occur. There will always be a number of freak accidents, and I can imagine a safety belt being a distinct disadvantage in some unless it came adrift or unfastened.

Some years ago, when driving alone, my car hit a high kerb after a skid on oil, the steering was damaged, the car turned 90 degrees, crossed the road, and dropped down a steep, rocky 60-feet (18-m.) river bank, landing upside down in the water with all windows except the rear one immediately submerged and no glass in any of them. The driving-seat, bench type, had broken free, but was itself undamaged. Escape was immediate through the back window as it filled with water. In this accident a safety belt might have been far from helpful.

Mr. A. W. Fowler (June 3, p. 1609) asks what advice should be given for use in skids or collisions. As soon as I knew a fall was imminent and saw where the car was to land, I lay down on the bench seat, pressed my face hard into the angle between the seat and the back, and held on tight—one hand on top of the back, the

other under the front of the seat. Although the seat came adrift from its attachments, and my passage downwards was far from smooth, I sustained some general bruising only. The roof of the car had, at one stage, hit a sharp rock, and the resultant deep cleft came well below the level where my head would have been had I been strapped into the seat.—I am, etc.,

Lancaster. IAN D. KITCHIN.

SIR,—Dr. A. Ward Gardner (May 20, p. 1463) raises the important point as to which type of safety belt should be worn in cars, and quotes whiplash injury to the neck as a contraindication to the use of the lap-strap combined with shoulder or diagonal restraint. It is no doubt true that this injury is possible, but Kulowski[1] and Schaefer[2] mention serious whiplash injury mainly in connexion with rear-end collisions. Hip-restraint alone would not prevent this injury, and, if experience were to show that it is more common with body restraint, that surely is an argument for a high seat-back rather than one against body-restraint.

The use of a lap-strap alone in British cars with their limited dimensions would give no protection against body-flexion and jack-knifing. In Kulowski's work, quoted by Dr. Gardner, head-on crash experiments by Severy *et al.*[3] are described, in which, even at an impact speed of 21 m.p.h. (34 kg.p.h.), a body with hip-restraint alone suffers jack-knifing with a forward head movement of about 28 in. (71 cm.). At an impact speed of 52 m.p.h. (84 km.p.h.) head movement was found to be of the order of 52 in. (132 cm.). In our cars even the lower speed would involve violent contact of the head with forward structures of the car, not to mention chest-contact with the steering-wheel. There seems little doubt, therefore, that some form of body-, as well as hip-, restraint is essential.

In these same experiments an impact as low as 21 m.p.h. produced a maximum lap-belt loading of 5,500 lb. I would therefore agree with Dr. Gardner's implication that the British Standard (No. 3254) of 4,000 lb. for the seat-belt assembly seems inadequate. In this connexion the maximum loading of the seat-belt in crash situations occurs within about 70–100 milliseconds, and yet the rate of application of the test-load according to B.S.3254 is such as to cause a movement of the test trolley of not more than 4 in. (10.2 cm.) *per minute* from no load to full load. Perhaps the British Standards Institution would enlighten us on this aspect, but I would not have thought that this test gives an adequate reproduction of the performance of a harness under crash conditions.

According to Severy, "in contrast with the three to four thousand pound, three inch belt (1¾ inch by British Standards) currently used by motorists, an 8,000 lb. loop strength, three inch wide nylon lap belt will increase motorist protection by:

(*a*) Reducing contributions to slack such as those identified as belt stretch and body deformation.

(*b*) Reducing restraining unit pressure applied by the lap belt to the motorist because of the greater surface area provided by a three inch belt.

(*c*) Providing a restraint having a loop strength more in keeping with the loadings encountered in automobile accidents and therefore less likely to fail during impact.

(*d*) Reducing front seat occupants' leg injuries by reducing belt elongation that permits the knees to contact the dash for moderately severe front-end collisions."

A full harness including lap-strap would in my view be the ideal, but when worn properly—that is, with no slack—would in many cars restrict driver movement—for example, applying a fascia-mounted handbrake. I would therefore suggest the use of an 8,000 lb. strength combined lap and diagonal belt, and would point out that independent tests have shown a combination near this specification to be available on the market.[4] From personal use of this harness, with anchorage points strengthened by 3 in. (7.6 cm.) diameter ¼ in. (3.2 mm.) steel plates, I can testify that driver-control is unhampered and that passenger-comfort and safety, particularly of children, are greatly increased.—I am, etc.,

Great Missenden, Bucks. D. W. ATKINSON.

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4 *Shoppers Guide*, 1961, No. 17. The Consumer Advisory Council, British Standards Institution.

Phenazocine and Respiratory Depression

SIR,—Several of your correspondents recently have been giving their views on the use of the analgesic drug phenazocine ("narphen") as an adjuvant to anaesthesia. Much of what has been written has been on the depressant effect of the drug on respiration, and it appears that no general agreement has been reached.

I have used this drug recently as the sole adjuvant to anaesthesia, according to the technique described by Swerdlow and Brown.[1] After induction of anaesthesia nitrous oxide and oxygen were given. When respiration started returning phenazocine was given—the initial dose, 0.5–2 mg., depending on body weight. Further doses were given, as judged necessary by movement, rapid respirations, etc., during the operation. In my series 51 patients have received this anaesthetic. The average respiratory rate was 14.6 (range 8–20) and the minimum respiratory rate was 10.8 (range 3–18). Ten patients had to be given "lorfan" (levallorphan) during operation because of undue depression of respiration. I agree, therefore, with the statements made by Dr. Ronald Shaw (March 18, p. 825).

In an attempt to avoid respiratory depression 43 patients so far have been given lorfan, 0.5–1 mg., before the initial dose of phenazocine was injected. The average respiratory rate in these patients was 16.2 (range 9–23) and the minimum respiratory rate was 13.3 (range 5–22).

Your previous correspondents on this topic have been using halothane, trichloroethylene, and even muscle relaxants in conjunction with phenazocine, and in my opinion the use of these agents will obscure, to some extent, the evaluation of the effect of phenazocine as regards analgesia and respiratory depression. In my series an attempt has been made to assess the usefulness of this drug, as a supplement to anaesthesia, without the interference caused by other drugs.—I am, etc.,

Salford Royal Hospital, Salford 3, Lancs. IAN P. MCEWAN.

REFERENCE

1 Swerdlow, M., and Brown, P. R., *Brit. J. Anaesth.*, 1961, **33**, 126.

Collapse from Reserpine

SIR,—It was good to see your annotation (April 8, p. 1022) on "Collapse from Reserpine," and I was particularly interested in one sentence: "Excretion of noradrenaline is reported to be reduced, but *no data are*

available to determine the lowest effective dose" (my italics). Recently we had a patient who collapsed suddenly after induction of anaesthesia; he had received "serpasil" (reserpine), 0.1 mg. b.d., for 13 days pre-operatively. A week later, after a sensitivity test with ephedrine, he was induced by exactly the same technique without any trouble. Could this small dose of reserpine have depleted his noradrenaline stores to such an extent? Why do some patients get into trouble with little trauma while others go smoothly through major procedures? Are there any other precipitating factors that we should keep in mind?—I am, etc.,

GWENDA M. LEWIS.
Christian Medical College and Hospital,
Vellore, S. India.

Headache and "Eyestrain"

SIR,—I should like warmly to congratulate Mr. H. Jackson on his letter relating to headaches and spectacles (May 6, p. 1316). The great F. D. Roosevelt once told a frightened world that, "The only thing we have to fear is fear itself." There can be few medical subjects to which this is more appropriate than the relationship between eyes and spectacles.

It is therefore all the more disturbing to find some of your correspondents indulging in niggling criticism of Mr. Jackson's basic thesis. No doubt every one of us can envisage specialized indications for the supply of spectacles. To mind come such reasons as commercial, psychiatric, and even plain vanity—while there may even be some more special indications with genuine medical value (e.g., protective). None of these alter the validity of Mr. Jackson's basic statement.

Your correspondents also ignore his original question. What is the evidence that minor errors of refraction cause headaches?—I am, etc.,

M. J. GILKES.
Sussex Eye Hospital
Brighton 7.

Examination of the Spleen

SIR,—I find the following technique very helpful in detecting minor enlargement of the spleen. The tips of the index, middle, and ring fingers of the right hand are inserted under the left costal margin while the left hand is applied to the lower ribs at the back, pushing them forwards. The patient is instructed to take a deep breath, at the end of which the fingers of the right hand are pushed still further up under the costal edge. While the patient expires, the right hand is gently but firmly moved down, pushing the spleen in front of it, whereby the edge can be easily palpated.

I do not know whether this method has been described before, but it is particularly satisfactory in children, especially in cases where the spleen can only be doubtfully tipped or is not palpable with the usual classical ways.—I am, etc.,

J. M. IBRAHIM.
Oldham and District General Hospital,
Oldham.

Leg Ulcers

SIR,—Drs. A. Girdwood Fergusson and J. C. P. Logan have written a timely article on local applications for leg ulcers (March 25, p. 871). They have found no new panacea, for eusol is no recent discovery—but it is good, always has been, and always will be. However, there should be whole-hearted applause at their advocacy of simple remedies.

The blandishments of salesmen and the flood of highly coloured advertising literature suggest that the local application is all-important. None of them emphasizes control of oedema or mentions the clinics where only cremor zinci is used. We all have admired, for instance, the advertisement showing the symphony orchestra symbolizing the perfect co-ordination of the ingredients of a certain application; but, on closer consideration, one realizes that the conductor of the orchestra controls the various groups and can silence the strings with a gesture or bring up the "winds" and so on, for maximum effect. No such choice or control is afforded the physician using this combined application. We are in danger of overlooking and being led away from fundamental principles. We seek wonder cures, but, alas, such do not exist. Drs. Girdwood Fergusson and Logan are to be congratulated on stressing these facts.—I am, etc.,

C. H. WICKHAM LAWES.
Sydney, Australia.

Gangrene of Penis

SIR,—Recently a patient of mine, aged 79, a retired lorry-driver who had been married 49 years and was childless, presented at the surgery with irreducible paraphimosis. He had suffered for four years from auricular fibrillation, and during the last six months from attacks of acute-on-chronic bronchitis. There was no oedema of the ankles, and the fibrillation was well controlled with digitalis. Dorsal slit was performed under local anaesthesia at the Huddersfield Royal Infirmary. Healing occurred satisfactorily.

Five weeks later I was called to see him, and found that he now had dry gangrene of the glans penis. It was noted that pulsation was present in the dorsalis penis artery. Although amputation was considered his general condition made operation inadvisable, and he died two and a half weeks later. My textbook of surgery[1] states that "gangrene of the penis occurs in debilitated old men without apparent cause." One wonders here why paraphimosis should occur at so late an age, and how gangrene could occur in so vascular an organ.

I am grateful to Mr. W. E. Thompson, under whose care the patient was admitted.

—I am, etc.,

S. L. HENDERSON SMITH.
Huddersfield.

REFERENCE

[1] Romanis, W. H. C., and Mitchiner, P. H., *The Science and Practice of Surgery*, 6th ed., 1937, Vol. II, p. 909. Churchill, London.

Management of Disseminated Sclerosis

SIR,—Your leading article, "Management of Patients with Disseminated Sclerosis" (April 29, p. 1222), presents a comprehensive survey of the therapy of this disease. I would like to comment on some additional items in treatment which are of current interest and which might be mentioned for the sake of completeness. Germane to drug therapy, the use of tolbutamide[1,2] might be mentioned, while it is emphasized at the same time that this is considered a controversial method of therapy, at which the manufacturers of the drug look askance,[3] as well as others.[4]

More significant, however, are the therapeutic benefits achieved through temperature manipulation, a subject of several recent communications. Boynton[5] and his co-workers have reported temporary improve-

ment in patients taking daily ten-minute cool baths (80° F., 26.7° C.). Similar benefits were reported by Watson,[6] who cited Boynton's work, as well as similar findings by others. Mead[7] has been favourably impressed with the improvement of multiple sclerosis produced by chilling of extremities. Finally, in one of your annotations[8] reports on this modality were favourably reviewed.—I am, etc.,

Memorial Hospital of Long Beach, Long Beach, California, U.S.A. GEORGE X. TRIMBLE.

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5 Boynton, L., Garramone, P. M., and Buca, J., *N.Y. St. J. Med.*, 1959, **59**, 3236.
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7 Mead, S., ibid., 1960, **262**, 1094.
8 *Brit. med. J.*, 1960, **1**, 1264.

Maternity Units

SIR,—The letter from Mr. J. Marshall Scott and Dr. R. G. Law (May 27, p. 1543) would, I think, be likely to mislead readers who did not attend the Congress, and who may not appreciate that Professor Norman Morris's paper was given in a discussion on the planning of hospital buildings. The custom in the Congress proceedings is that speakers issue their papers in advance and amplify and comment upon them at the sectional meetings.

In presenting his paper Professor Morris referred to a number of unsatisfactory features which were still apparent in existing departments, but he spent some time in references to the improvements which had been made in the past year or so in existing departments and in the human relations within them. In the discussion which followed no speaker disputed the need for further improvements, and contributors included representatives of many groups—members of hospital authorities, nurses, hospital administrators, and an official representative of the Royal College of Obstetricians and Gynaecologists.—I am, etc.,

F. J. FOWLER,
Recording Secretary, Hospital Section, Royal Society of Health Congress, 1961.
London S.W.1.

Cigarette in the Mouth

SIR,—The letter from Mr. John Dark and others (May 27, p. 1541) suggests a factor in the incidence of lung cancer related to the number of times a cigarette is *lit* rather than the number of cigarettes *smoked*. Logically this points to the means of lighting the cigarette, and I have noticed that heavy cigarette-smokers tend to light "off the flare." Anyone who is not hardened to this will be horrified at the filthy taste of the fumes from the burning match-head. Are these chemical vapours carcinogenic? It would be interesting if Mr. Dark and his co-workers were to inquire further into the lighting habits of patients with bronchial carcinoma, dividing them into those who light "off the flare," those who light a match and let it burn well first—as pipe and cigar-smokers do—and those who use a cigarette lighter.

But, if they find any really significant results, I hope they will let me know privately before they publish them, so that I may quietly buy shares either in the lighters or in the matches!—I am, etc.,

Great Dunmow, Essex. GEOFFREY BARBER.

Favism

SIR,—In your leading article (May 13, p. 1377) you refer to favism as "this ancient disease." Pythagoras was born in Samos and established himself at Croton, both places being in areas where favism is endogenous.[1] He made it a rule for his disciples to abstain from beans, and there is evidence that the same rule was obeyed by earlier sects.[2] May not this religious law have been based on medical observation, like the Jewish abstinence from pork?—I am, etc.,

Clinical Pathology Department, University College Hospital, London W.C.1. A. F. FLEMING.

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1 Whitby, L. E. H., and Britton, C. J. C., *Disorders of the Blood*, 1957, 8th ed., p. 104. Churchill, London.
2 Burnet, J., *Early Greek Philosophy*, 1892, p. 104. Black, London and Edinburgh.

POINTS FROM LETTERS

Hallux Valgus

Dr. W. R. E. HARRISON (Buxted, Sussex) writes: It was fascinating to read Mr. G. N. Golden's article (May 13, p. 1361) about a new operation to correct that self-inflicted deformity hallux valgus; but one's pleasure was soon turned to pain by the associated mental picture it aroused of sex-linked shoe imposed upon adolescents by the trade. And then one's mind harked back to those brave new words spoken about "Prevention" during the inception of the N.H.S. only to be whittled down to "Welfare" as soon as the deal had been completed. Welfare is popular: prevention is not. Ah, there's the rub! A new metabolic dyscrasia is discovered (somethinguria, I forget its name). This disorder may produce one idiot or perhaps two per annum per county, but being genetically linked is self-limiting if left alone. Against this gnat Publick Health opens up its big guns at considerable publick time and expense; but on the question of the universal shoe, which bears no resemblance to the universal foot, it keeps quiet.

Second Ectopic Pregnancy

Dr. D. H. BARHAM (Kwahu Hospital, Mpraeso, Ghana) writes: Dr. A. H. Bartley's letter (April 29, p. 1252) prompts me to report a further case of my own. The patient is Ghanaian, aged 21, para 2. She was admitted to hospital as an emergency on June 6, 1961, with acute sudden abdominal pain, rapid feeble pulse, cold and sweating. The abdomen was slightly distended, and marked rebound tenderness was elicited. A previous laparotomy scar was noticed, which, the patient stated, was performed in 1959 when "a three months' pregnancy got spoilt." She denied she was now pregnant, as her last menstrual period had occurred only three weeks previously. However, I advised immediate laparotomy, and found a ruptured ectopic pregnancy in the interstitial part of the left Fallopian tube. The right tube and ovary were missing as a result of the previous operation.

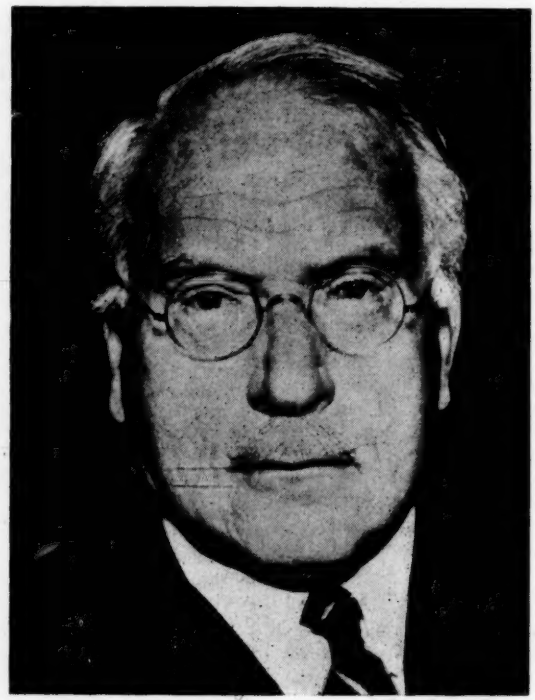
Neonatal Resuscitation

Dr. L. G. HULL (Doncaster, Yorks) writes: Dr. W. N. Leak's experience with "cardiazol-ephedrine" (leptazol and ephedrine), published in the *Practitioner* (1953, **171**, 653), prompted me to obtain the drug. Since then I have had two cases when the emergency arose. On the first occasion the drug promptly revived a flaccid, lifeless, deep-blue-grey baby after it had been in that condition for several minutes, during which time all measures available had been tried, and further time had been lost in a frantic search in my car for the drug I had bought 18 months previously and forgotten. On the second occasion it was the first thing I gave, for this time the drug was where it should have been—in my bag. The response was immediate and as dramatic. In my limited experience I have seldom been so impressed.

Obituary

C. G. JUNG, M.D., LL.D., D.Sc.

The death of Professor C. G. Jung on June 6, aged 85, removes one of the great pioneers of modern psychology, whose ideas on the functioning of the mind, and particularly the unconscious mind, had a world-wide influence. He was a prolific writer, a clear and witty speaker in several languages, and an impressive figure, but he retained all his life the humility of an inquiring and kindly physician. Despite a subtle intellect, a well-stored memory, and an interest in remote cultures, his friendship seemed to those privileged to share it to be marked by a happy simplicity.



[Press Portrait Bureau

Dr. E. A. BENNET writes: Carl Gustav Jung, the son of a Lutheran clergyman, was born in Kesswil, Northern Switzerland, in July, 1875. Later his father was transferred to Basle; there Jung went to school, and, entering the University of Basle, he qualified in medicine. His family had close association with the ancient university: his grandfather held the chair of medicine, and Jung himself was subsequently appointed professor of psychiatry in the university. Jung's interest in psychiatry was aroused by reading the introduction to Krafft-Ebing's book on mental disease, and there and then he decided to study the subject. This shocked his teachers, for in those days psychiatry was off the main road in medicine. His decision involved the refusal of an attractive offer to become assistant to one of his professors, recently appointed professor of medicine in a German university. Instead Jung joined the staff of the Burghölzli Hospital in Zürich, and there, under Professor Eugen Bleuler, he remained for eight years, becoming eventually senior staff physician and instructor in psychiatry at Zürich University.

Jung found the progressive atmosphere of the Burghölzli to his taste. Bleuler had built up a team of enthusiastic young doctors engaged on clinical and laboratory research with special reference to the aetiology and treatment of dementia praecox—now named schizophrenia—the commonest mental disorder. Jung was one of the first psychiatrists to combine psychological and physiological methods of research. To begin with he cut and studied brain sections, hoping to discover pathological lesions that might throw light on the pathology of dementia praecox; but these investigations were fruitless. He then used Galton's word-association test and devised techniques for the simultaneous recording of respiration, heart rate, and the response to the psychogalvanometer. It became certain that the results of the word-association test were influenced by emotion—of which the person being tested was unconscious—and that alterations in physiological functioning varied concurrently with the emotional changes.

Jung coined the term *complex* to describe the constellation of hidden, unconscious ideas responsible for these fluctuations. Psychologists and psychiatrists the world over have accepted the term and it has even found its place in the *Oxford English Dictionary*, where credit for it is given to Jung. But why had the complex become unconscious? Pierre Janet's work on the dissociation of ideas, thought Jung, might give the answer. He had met Janet in Paris, and, although not one of his pupils, he had heard him lecture. While appreciating his clinical acumen, he found his theoretical formulations unsatisfactory, and Janet's work was of no help in solving the meaning of the complex, nor had it any influence on Jung's later work. After considering other theories, Jung decided that Freud's theory of repression gave the answer to the problem. At once he wrote to Freud telling him of the experimental proof of his theory of repression.

Publication of his studies on word-association and his volume *The Psychology of Dementia Praecox* established Jung's reputation as an original thinker. He sent a copy of this book to Freud, and this led to an invitation from Freud to visit him in Vienna. The two pioneers met for the first time in 1906. They had a talk lasting 13 hours! Their prolonged discussion was due to Jung's determination to see Freud's point of view. Jung was much impressed by Freud and recognized him as a genius; nevertheless his admiration did not mean that he accepted Freud's teaching *in toto*. For example, the insistence on the fundamental importance of the infantile sexual trauma was totally unacceptable. Their collaboration—not always harmonious—lasted until the publication, in 1913, of Jung's *Psychology of the Unconscious*.

Freud did not agree with the conclusions in this book, particularly those on symbolism and on the nature of the unconscious. This unexpected situation astonished Jung, feeling as he did that anyone observing the facts he had observed was bound to take them seriously and at any rate discuss them objectively. Yet Freud thought otherwise and expressed his disapproval in no uncertain terms. Jung was bitterly disappointed; but, as the air cleared, he came to see that there must be a reason for Freud's decision, apart from personal considerations or prejudice. As a scientific thinker, he was determined to study the enigma of their inability to work together. Eventually the result of his reflections appeared in *Psychological Types*, perhaps his most widely known book, where he identifies two main groups of human beings—extraverts and introverts. This by no means rigid grouping indicated the predominant direction of mental energy (libido) in each type; he also described their differences in functioning, especially in thinking, feeling, sensation, and intuition. A person of extraverted type was bound to approach the contingencies of life in one way, whereas the introvert would see them from another angle. Here, briefly, was the key to the problem of the Freud–Jung break: Freud, the typical extravert, and Jung, the typical introvert, were fated to see clinical and other problems differently. That Jung's typology is sound is evidenced

by the fact that it became widely accepted by psychologists. To-day the man-in-the-street has an idea of what the terms mean and uses them constantly, although unaware that Jung introduced them.

Jung himself considered his hypothesis of the *collective unconscious* as his most important contribution. We trace the ancestry of the body without hesitation: why not that of the mind? Instincts, for example, are inborn and certainly not personally acquired through education and training. Jung demonstrated the patterns—that is, the archetypes—in which the unconscious appeared autonomously in objective, collective form. Thus the mind possessed an impersonal as well as a personal "layer" in the unconscious. Jung's hypothesis—he detested dogmas!—has often been misunderstood and misstated, for his critics, unfortunately, have not always troubled to read what he has written on the subject. For centuries the notion of archetypes had been accepted. Jung did not invent this concept; but he applied it to the study of human psychology where previously a purely personalistic outlook had been taken for granted.

Jung attached the highest importance to established facts and he was never interested in theories as such. Had anyone produced a more satisfactory explanation than his own for the facts explained by the hypothesis of the collective unconscious, Jung would have welcomed it.

In analytical psychology great importance is given to the investigation of dreams, and this surprises some psychiatrists. But Jung, faced with the mystery of psychological illness, had no option in the matter. We must take facts as we find them: people do dream, and experience showed that the analysis of the dreams was often of importance in bringing about a cure. For Jung the unconscious, personal and impersonal, was a fascinating study. It amazed him that thinkers such as Freud and Adler were prepared to be dogmatic about the functioning of the unconscious. Jung was convinced that psychology, a very young science, was by no means ready for such final pronouncements.

As a lecturer Jung was in the first rank. His sincerity, naturalness, and modesty made an immediate impact on an audience. He really believed in what he said, for he spoke out of his own experience. Therein resided his power. Mountaineering and sailing appealed to him as a younger man, and in later life he found recreation in the tougher side of gardening—digging, cutting down trees, chopping up firewood. But his research into human psychology always came first, and this lay behind his interest in travel. He spent months in Africa studying the minds of the primitive people among whom he lived and journeyed. He also visited India and the United States, and he often came to England. His travels supplemented his research, for he had an observant eye, often noting features in the customs and habits of highly civilized as well as primitive people which escaped the mere tourist.

An edition of Jung's collected works is in preparation and eleven volumes have already appeared in English. A German edition is also being published, and it is interesting to note that one of its three editors is his daughter, Marianne Niehus-Jung.

Family life was always of central importance to Jung. In 1903 he married Emma Rauschenbach, and they had five children: all have married and there are nineteen grandchildren and ten great-grandchildren. Mrs. Jung, who died in 1955, was deeply interested in her husband's work. She became an authority on the legends of the Holy Grail and her work has recently been collected and published.

Throughout Jung's books emphasis is laid on the purpose, the aim of life. He was free from the blight of determinism. In his clinical work treatment was directed towards current problems, their meaning, and their purpose. Important though past experiences might be, illness could only be cured in the present. Constantly he addressed himself to the question: Why did this person become ill at this time and in this way? Further, he sought the nucleus of healthiness, wholeness, in his patients and saw neurosis as a disturbance of normal individual functioning and not as an entity in its own right.

Many find Jung's later works difficult. Jung himself would agree; he was writing of obscure matters, and, as always, he went by the facts. Nature seldom presents her secrets in easily comprehensible terms, and understanding demands hard work. Over many years and in many fields of knowledge Jung's contributions have had a fertilizing effect. His reputation as a thinker, now great, will be greater still as his ideas come to be seen in their true perspective, freed from the transient controversies of the past.

EDWARD COTTER, C.I.E., M.B., B.Ch., D.P.H.

Colonel Edward Cotter, formerly of the Indian Medical Service and Public Health Commissioner with the Government of India, died in Dublin on June 2. He was 68 years of age.

Edward Cotter had a most distinguished career in the Indian Medical Service. Born in Ireland, son of the late Eugene Cotter, of Blarney, Co. Cork, he was educated at University College, Cork, and qualified M.B., B.Ch., B.A.O. of the National University of Ireland in 1915. He entered the Indian Medical Service in 1915, and served in the first world war in Mesopotamia and Persia. In 1923 he took the D.P.H. and began his hygiene career when posted to Army Headquarters in 1924, becoming Deputy Assistant Director of Hygiene and Pathology in 1925. In 1930 he was transferred to civil employment as Assistant Director of Public Health in Burma. In 1934 he was promoted to be Director of Public Health in Burma, and his vigorous and lively personality made itself felt throughout the country.

Cotter was transferred to Delhi in 1937 as Deputy Public Health Commissioner with the Government of India. His services were used on many occasions to represent India at overseas conferences and on the permanent committee of the Office International d'Hygiène Publique in Paris. In 1939 he was appointed Public Health Commissioner with the Government of India, and bore with distinction the heavy burden of public health administration throughout the anxious years between 1937 and 1947. The Indian Members of Council and Ministers under whom he worked were greatly impressed by his industry and grasp of the problems involved and by his genial and friendly personality. He was officially reported on as having "contributed notably to the advancement of health administration in India." Since retiring in 1947 Cotter settled down in Dublin, where he was on the administrative staff of the Irish Medical Association.

Teddy Cotter was a lively, lovable, genial Irishman, clubbable, volatile, and full of enthusiasms. He had a wide range of friends in many fields—and no enemies. Sympathy is extended to his wife and son.—G. R. McR.

C. G. NAIRN, M.B., Ch.B., F.R.C.S.Ed., M.R.C.O.G.

Dr. C. G. Nairn died suddenly on June 1, aged 46 years. He was the only son of the late Dr. and Mrs. R. W. Nairn, of Farnsfield, Notts.

Charles Godfree Nairn graduated M.B., Ch.B. at Glasgow in 1938, and obtained the F.R.C.S.Ed. in 1948, becoming M.R.C.O.G. in the same year. He was consultant obstetrician and gynaecologist to the Prince of Wales, he Bearsted Memorial, the German, and the East End Maternity Hospitals. During the war he served as a squadron leader in the R.A.F.V.R.

Mr. ALBERT DAVIS writes: The sudden death of Charles Nairn at such an early age has come as a shock to his many friends and colleagues. He was at the height of his powers, both physically and mentally, and it is difficult to believe that his cheerful and happy personality is no longer with us. We worked closely together for many years at the

Prince of Wales Hospital in Tottenham, and it was during this time that he developed to the full the Wertheim legacy left there by Aubrey Goodwin. His subsequent reputation as a surgeon was indeed based on his facility in this particular operation, and the long-term results he obtained by the radical block-dissection method he perfected are probably superior to most others. He was also an excellent obstetrician of much ingenuity, and his manipulative skill with the forceps was widely known and admired. He was also an excellent teacher, both of nurses and of post-graduates. Though Scottish (and proudly so) in origin, Nairn was actually the epitome of the typical Englishman. Hearty and cheerful in manner, his bluff exterior concealed a wealth of kindness and consideration for others which was reflected in the personal affection he inspired in everyone, patients and colleagues alike. His loyalty and personal integrity were unquestioned, and he was indeed incapable of a mean action. He loved the country and its sports, at several of which he was adept, and was a connoisseur of good living in all its best aspects. Our sympathy goes out to his devoted wife and daughters, who were indeed the happiest aspect of his life.

MYER COPLANS, D.S.O., O.B.E., M.D., D.P.H.

Dr. Myer Coplans, who lived in Hendon for many years, working there as a bacteriologist and biochemist, died on March 9 at the age of 82.

Myer Coplans was born on January 12, 1879, the son of the Rev. Michael Coplans. He studied medicine at University College, London, and Guy's Hospital, where he won the senior natural science scholarship. He graduated M.B., with honours, in 1901. Three years later he proceeded M.D. and took the D.P.H. of Cambridge. After graduation he served as a civil surgeon in the South African Field Force. On his return to Britain he worked in the public health service for a time and then became demonstrator in bacteriology and public health in the University of Leeds, and was the author of an article in this journal in 1905 on the subject of the medical inspection of elementary school-children. Elected to a Beit memorial fellowship in 1913, he carried out research on immunity at the Lister Institute.

As a Territorial officer he served with distinction throughout the first world war. While at Leeds he had undertaken investigations for the War Office on water purification in the field, and his first post in the Army was that of commanding officer of the first mobile hygiene laboratory in the B.E.F. As sanitary officer to the Second Army he had much to do with the control of typhoid fever among the Belgian population. Later he became A.D.M.S. (Sanitation) at the headquarters of the Italian Expeditionary Force. Awarded the D.S.O. in 1917, he was appointed O.B.E. in 1919 and was the recipient of honours from the Belgian and Italian Governments. Later he served on the Chemical Warfare Committee of the Medical Research Council, and he was also technical consultant to the Laboratoire des Vaccins Pasteur (pour l'Etranger), Paris.

After the war he was again elected to a Beit memorial fellowship, and came to live in Hendon, carrying out much pharmacological, biochemical, and bacteriological research during the following years, and writing on such subjects as vaccinia and variola, the use of immature rabbits as experimental typhoid carriers, and the chemistry and pharmacology of acetylsalicylic acid. He was a man of independent mind, and on some matters his strong views by no means met with general approval. But he was a keen and active worker for the B.M.A., being the prime mover in the formation of the Hendon Division, of which he was honorary secretary for several years and chairman in 1937–8. Many years before that he had been awarded several scientific grants by the Association, and at the Annual Meeting in Brighton in 1913 he was vice-president of the Section of Bacteriology and Pathology. With his death the last of the doctors who lived and worked in Hendon when it was a village has disappeared.

Dr. Coplans leaves a widow, a daughter, and a son, Surgeon Captain R. M. Coplans, of the Royal Australian Navy.

G. M. GRANT, M.B., Ch.B.

His many friends and colleagues in the eastern region of Scotland were shocked and grieved by the news of Dr. Grant's death, which occurred on May 8 in a motoring accident. He had retired from private practice in Dundee only two weeks earlier, and, accompanied by his wife, he was on the first stage of a journey to Canada to visit their two sons there. He was 68.

George Murray Grant was born in Nelson, Lancashire, but was brought up in Dundee, where he attended the High School. He studied medicine at the Dundee Medical School and graduated M.B., Ch.B. at the University of St. Andrews. After service in the R.A.M.C. during the first world war, he returned to Dundee to take up an appointment in the physiology department and then to start in general practice in the city. While thus engaged, he was appointed assistant radiologist at Dundee Royal Infirmary in 1923. In 1933 he was promoted to be radiologist, having commenced private practice in the interval. He retired from the Infirmary in 1960 but continued private practice for another year.

His opinion as a radiologist was much esteemed by those who sought it, and he was held in high regard by his colleagues in and out of hospital. The hospital board of management thought much of him, and on his retirement they appointed him consultant emeritus to the Infirmary, which was an appointment that gave him much pleasure.

During the last fifteen years he served the Dundee Branch of the B.M.A. as Honorary Treasurer. Only a few days before his death he was met by some of the Branch members, who presented him with a silver cigarette-box as a mark of the appreciation and good will of the Branch. He loved the society of his friends and colleagues, giving great support to the Dundee Medical Club, of which he was a past-president. He had been a member of Rotary since 1934.

Those who knew him will remember him always with great affection and respect, and they extend their deep sympathy to his wife and family.

WILLIAM DAVIDSON, M.B.

Dr. W. Davidson died suddenly on May 10. He was the elder son of Mr. and Mrs. W. Davidson, of Perth.

William Davidson graduated M.B., Ch.B. at St. Andrews University (Dundee) in 1943. He took on an assistantship in Forfar for six months, and was appointed house-surgeon and ear-nose-and-throat house-surgeon at the Royal Infirmary, Perth, in 1944. As a captain in the R.A.M.C. he served in the Orkneys in 1946. The following year he was an assistant in a practice in Shropshire, and finally became a partner with Dr. Robert Ritchie in Perth in 1948.

Willie—as he was known in Perth—personified the true family doctor, and since coming to Perth quickly made a niche for himself. Not only was he a wise and able physician but a lovable personality. He was a happy man, devoid of any guile and incapable of doing anyone a wrong. He was beloved by his patients, to whom he was not only their family doctor but a warm-hearted friend, interested in all their problems and ever ready to give what help and advice he could. No one could ever doubt his integrity, and both as a man and as a physician he won the respect of his colleagues and patients alike. Dying at the early age of 41, his life was short, but what an immense amount of good he accomplished in that time.—A. H. H.

A. P. AGNEW, M.B., C.M.

Dr. A. P. Agnew, who retired in 1949 after being in practice for 58 years, died at the home of one of his daughters in Palmers Green, London, on May 11. He was 91 years of age.

Alexander Percy Agnew was born on December 18, 1869, and was educated at Glasgow High School and Glasgow University. He graduated M.B., C.M. at the University of Glasgow in 1890. From then on until the inauguration of the National Health Service in 1948 he was in general practice, at first in Padiham, near Burnley, and then in Wymondham, Norfolk. His son, Dr. Alan P. Agnew, who died in 1957, joined him in practice in Padiham, though later he became senior consultant physician to the South Ayrshire group of hospitals. After the first world war Dr. Agnew senior moved to Wymondham, remaining there for 30 years until beginning his well-earned retirement at the age of 79. For more than 20 years he was medical officer of health of St. Faith's and Aylsham, Forehoe and Hemstead rural district councils, and Wymondham urban district council. Dr. Agnew was married and had five children. He is survived by two daughters, four grandchildren, and three great-grandchildren.

D. H. writes: I knew Dr. Agnew only in his retirement, but such was the esteem in which all his past patients held him that it was not difficult to build up the picture of his professional life. When my husband and I stayed in Wymondham in recent years it was sufficient to introduce our small son as " Dr. Agnew's great-grandson " for recognition to be immediate and reminiscence heartfelt. Similarly, in Padiham, years after both he and his son had left to take up other work, we met someone who could remember " the beloved physician " of her childhood who always found time for a story and a joke to brighten the sick-room. His interests were wide, and even a few weeks before his death he was intent on the sports programmes on T.V. and radio. He loved the garden, and would take great pride in pointing out to visitors especial favourites among the flowers. Most striking of all was his alertness to new developments in medicine. Earlier this year he followed the progress of his youngest grandson, who has coeliac disease, with concern and interest; medical textbooks from previous decades were produced in a discussion of the changes in prognosis and treatment. But even more than this he will be remembered for his interest in, and love for, people. Every member of his family was close to his heart, and he belonged to a generation who deemed it a pleasure to keep in touch with them all. They, and his many friends, will mourn his passing.

W. D. KEYWORTH, M.D., M.R.C.P.

Dr. W. D. Keyworth, who came to a country practice at St. Mary Bourne, near Andover, after retiring from the Indian Medical Service with the rank of lieutenant-colonel in 1937, died on May 12 in a nursing-home near Winchester. He was 80 years of age.

William David Keyworth was born on January 31, 1881, the son of missionary parents. He went to Cambridge as gold medal scholar from King's Lynn Grammar School, and won another scholarship to Charing Cross Hospital. Graduating B.Ch. in 1906, he took the M.B. and the M.R.C.P. a few years later and proceeded M.D. in 1928. After qualification he held among other appointments at his teaching hospital those of house-physician and house-surgeon and then entered the Indian Medical Service, in which he had a distinguished career. During the first world war he was one of the survivors of the siege of Kut.

He came to St. Mary Bourne in 1937. He could scarcely have foreseen how fully occupied he would be for the next twenty years. Accustomed to Service life and discipline, he rapidly organized his life and his household around his new practice, and allowed few outside interests to interfere with continuous attention to his patients. Thus he established a standard of care which will not be forgotten in the Bourne Valley. He found time to serve on the local insurance and panel committees and, later, on the local medical committee and the executive council of the National Health Service. He represented the Winchester Division at Annual Meetings of the B.M.A. in 1945, 1946, and 1947. In the difficult days of 1948 and 1949 his able chairmanship of the Division will be remembered by many colleagues in the district. For many years until his death he was the president of the local branch of the British Legion.

Always athletic and a keen country walker, he was much distressed during the latter years when he was unable to walk without the greatest discomfort. His wife was as beloved as he was: they were inseparable, and her death in 1960 following shortly after his retirement from National Health Service practice left him disconsolate: they had no children. The joy and purpose of his life had been accomplished, his remaining strength seemed suddenly to leave him, and he died in the care of the Sisters of Bon Secours at Crawley.—J. W. E.

A. S. MACTAVISH, M.B., Ch.B.

Dr. A. S. Mactavish, who practised in Penrith for 48 years, died in hospital at Carlisle on May 11, aged 78.

Alexander Stuart Mactavish, the son of a Presbyterian minister, was born at Morebattle, Roxburghshire, on October 4, 1882, and was educated at George Watson's College, Edinburgh. He studied medicine at Edinburgh University and graduated M.B., Ch.B. in 1906. The following year he entered general practice in Penrith and continued to practise there until his retirement in 1955. He devoted his life to his patients and was much beloved by them, both as a friend and as a family doctor. He was admired by his colleagues for his ability and for his principles.

In 1910 he founded the local V.A.D., and during the first world war did valuable work as surgeon in charge of a local hospital for wounded soldiers. He was Medical Officer of Health for Penrith for several years, and in later life took a keen interest in the welfare of the aged. He was the first chairman of the Old People's Welfare Council. His main interests outside his work were fishing, golf, amateur dramatics and hockey, for which he was capped for Cumberland.

His colleagues extend their sympathy to his widow and two sons.

C. de L. SHORTT, M.D.

Dr. Cecil de Lisle Shortt died at his home at Kingston-on-Thames on May 24, aged 65.

" Dick " Shortt, as he was known to his friends, was born in Horetown, Co. Wexford, Eire, the son of the late Rev. Dr. C. de Lisle Shortt. He entered Trinity College, Dublin, in 1915, but very soon afterwards he joined the Army. He served in the Royal Garrison Artillery, the Royal Field Artillery, and later he joined the Royal Flying Corps on its formation, and served until he was invalided out in 1918. Badly gassed, it took him a year to recover his health, but he ultimately returned to his medical studies.

On qualification in 1922 he became house-surgeon at Yarmouth General Hospital, and later R.M.O. at the Preston Royal Infirmary. He then went into general practice in Clitheroe, Lancashire, where he remained until 1935. While in Clitheroe, as well as being a most successful general practitioner, he took a very active part in the corporate and civic life of the town. He was elected a county councillor, and among other works he was the founder of the Clitheroe Community Centre for unemployed men.

Owing to the stress of work in his practice, and the fact that his war disability was affecting his health, he moved

to a practice in Kingston-on-Thames. As a member of the Territorial Army he was called up to serve at the beginning of the second world war. He was first a company commander in a Field Ambulance, and later was senior medical officer of a troopship. However, his first war disability again caused him to be discharged from the Service in 1944, and after a period of convalescence he returned to his practice in Kingston.

Colleagues write: Dick Shortt was a wonderful man, so kind, understanding, and patient. He gave great comfort to the lonely and afflicted. His later life, being restricted to some extent by his disability, was devoted to the care of his practice, to him an absorbing interest and a source of inspiration. His clinical judgment was exceptional, and his standard of medical treatment of the best. He will be remembered with respect and esteem by all his colleagues and patients. Our deep sympathy goes out to his wife and family.

ALLAN WALKER, M.B., B.S.

Dr. Allan Walker, a medical officer of the Ministry of Pensions and National Insurance, died suddenly at his home at Padiham, Lancashire on May 25, aged 50 years.

Allan Walker was the fourth generation of doctors supplied by the male members of his family, his grandfather being one of Lister's house-surgeons at Glasgow Royal Infirmary. His father, the late Dr. L. H. Walker, practised at Seaton Delaval, Northumberland. After graduating M.B., B.S. at Durham University in 1937, he held the appointment of house-physician at the Sick Children's Hospital, Newcastle upon Tyne, followed by that of house-surgeon to the District Hospital, Ashton-under-Lyne. On the outbreak of the second world war he joined the R.A.M.C. and served until November, 1945, with a period of service in France in 1940. Demobilized with the rank of major, he took up the post of obstetrics officer at the General Hospital, Newcastle upon Tyne, for a period. He then decided to enter private practice, as all his medical forebears had done previously, and acquired an old-established practice in Padiham, Lancashire. For fourteen years he served his patients according to the highest traditions of the family doctor. He was also works medical officer to one of Lancashire's new industries.

Last year Dr. Walker realized reluctantly that he would be physically unfit in the future to continue to give the same high service to his patients, so he applied for and obtained a less exacting post with the Ministry of Pensions and National Insurance at Leeds and relinquished his practice. He had only taken up duties in his new post for one week when he was stricken with the illness which proved eventually fatal. The affection and devotion of his patients were shown by the crowded church at his funeral service and the panegyric delivered by the blind vicar, who himself had been one of the deceased's patients.

Dr. Walker leaves a widow and young family of one son and two daughters.—G. B. M.

H. J. SHORVON, M.B., B.S., D.A., D.P.M.

The obituary of Dr. H. J. Shorvon was published in the *Journal* of May 27 (p. 1546).

Dr. DUDLEY M. BAKER writes: Dr. H. J. Shorvon, over the last five years, has advised and treated many of my patients. A wonderful friend to them and to me, he was an utterly dedicated man, and I never knew him turn away when help was asked of him. We know now that he gave this, suffering as he was from a prolonged and fatal illness, and we can only describe his conduct on all occasions as utterly selfless. Those of us who were privileged to know "Joe" will find the gap in the panel of friendly consultants which we built up over the years very difficult to fill in quite the same way.

R. H. ENOCH, M.R.C.S., L.R.C.P.

The obituary of Dr. R. H. Enoch was published in the *Journal* of April 29 (p. 1259).

D. P. G. writes: Bob Enoch will always be remembered by those who served with him at the Royal Naval Hospital, Barrow Gurney. He was the senior anaesthetist and senior officer in the operating theatre team, the efficiency of which owed much to his tact and common sense. It was the custom for the principal surgeons to be given a "break" during heavy operating days, when the E.N.T. surgeon, ophthalmologist, and medically qualified dental surgeon would clear the list of some of the more usual procedures. During these occasions Enoch showed himself to be a very sound surgical technician. He was a very loyal colleague, and an extremely practical and unfailing friend. The devotion of his family life and the warmth of his hospitality will always be recalled with gratitude by all who knew him well. Bob Enoch spent his life trying to make life as easy and as comfortable as possible for all with whom he came in contact. He was a natural doctor and a natural gentleman. His wife and stepchildren will be joined by many in their sorrow.

Dr. RODERICK J. MACDONALD died recently at St. Peter's Bay, Prince Edward Island, which lies in the southern part of the Gulf of St. Lawrence. The last of the Macdonald family which came to Prince Edward Island from Inverness in the early part of the nineteenth century, Dr. Macdonald was 103 years of age.

We regret that Dr. T. Harold Pettit's name was wrongly spelt in last week's *Journal* (p. 1691).

Medical Notes in Parliament

QUESTIONS IN THE COMMONS

Pay Withheld for Breach of Contract

Mr. M. LIPTON (Brixton, Lab.) asked the Minister of Health on June 12 how many doctors and dentists, in each of the past three years, had had their pay withheld for breach of duty under the National Health Acts; and what were the total sums involved. Mr. E. POWELL: 86, 81, and 120; £3,941, £3,978, and £3,914. Mr. LIPTON commented that that information would be useful for the adjournment debate he was initiating on June 16 on the naming of guilty doctors and dentists. He asked the Minister to confirm that although the names of offending doctors and dentists were supposed to be secret a newspaper that wanted to publish them was not breaking the law if it did. Mr. POWELL replied that that was not for him to say.

Voluntary Mental Patients and Security

Mr. R. SORENSEN (Leyton, Lab.) asked what information the Minister had to show the beneficial or the adverse consequences ensuing from the increase in the number of voluntary mental patients; and, approximately, what was the number or percentage of those patients who curtailed such treatment against medical advice. Mr. POWELL said there was wide agreement that the removal of unnecessary restrictions on psychiatric patients was beneficial to them. The information asked for in the second part of the question was not available.

Mr. SORENSEN asked if it would not be worth while to find this information. Was the Minister satisfied that there was no release of patients with psychopathic tendencies? Mr. POWELL said he did not think any useful purpose would be served, because none of these men would be able to be compulsorily detained. The duties imposed by the Mental Health Act required those on whom they were imposed to take into account the risks involved.

Mr. T. L. IREMONGER (Ilford, North, Con.) asked if the Minister was aware of the serious implications in the question. Ronald Sowle, who was charged on April 27 with the murder of a 17-year-old girl in Bristol, had discharged himself from custody in circumstances in which he was detainable under the Mental Deficiency Act. If we got this wrong, and if the Act was wrongly administered, the public were going to lose confidence in it. Mr. POWELL said he must not refer to the specific matter because it was *sub judice*, but in general he recognized that attention to security must be the price one paid for the opportunity to carry out a liberal and enlightened policy.

Postgraduate Developments in London

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked the Minister which existing postgraduate medical schools would be incorporated into the proposed new teaching hospital in Chelsea. Mr. POWELL asked him to await a full statement on this matter which he intended to make shortly. He said this would be not later than the end of the month, and might be a little earlier.

Birmingham Maternity Hospital

Mr. D. HOWELL (Small Heath, Lab.) asked if the Minister was aware that the governors of the United Birmingham Hospitals had decided to reduce the number of confinement cases at the Birmingham Maternity Hospital by 500 a year; and what consultations had taken place with the Birmingham Regional Hospital Board before this decision was taken. Miss EDITH PITT, Parliamentary Secretary, replied that the reduction aimed at was about 300. It would not be in the interest of the hospital service to disclose communications between boards.

Mr. HOWELL described the answer as very disquieting. One of the great difficulties in the hospital service, particularly in the Birmingham area, was the complete lack of liaison between the governors of teaching hospitals and the Birmingham Regional Hospital Board and the hospital management committee. To take this action unilaterally was an act of social irresponsibility. Miss PITT would not agree with that. It was because the board of governors felt responsible for this maternity hospital—which took difficult cases—and to allow it to cater for emergencies, that it felt it necessary to take this step. Mr. K. ROBINSON said it was impossible for a regional board to carry out its planning responsibilities unless there was the closest liaison with boards of governors—which in the Birmingham region was non-existent. Miss PITT accepted the first point, but did not agree with the second.

Medical Vacancies in Newcastle Region

Mr. C. GREY (Durham, Lab.) asked how many medical posts in the Newcastle Regional Hospital Board area remained unfilled; and how many posts had been vacant for longer than two months. Miss PITT: 33 and 24, excluding non-teaching hospital posts below registrar for which the figures were not available. Mr. GREY thought one of the main reasons for the long waiting-lists was that the establishment was inadequate, and asked for further inquiries. These Miss PITT agreed to make, but pointed out that in March last year vacancies in the grades of registrar and below for Great Britain averaged 9% and the average for Newcastle was slightly below that.

Shortage of Consultant Psychiatrists

Mr. GREY also asked how many psychiatrists were required in the Newcastle Regional Hospital Board area; and when these doctors would be available. Miss PITT said the board had proposed to create four additional consultant posts. The Minister had approved two, which the board expect to fill in the next two months. Mr. GREY said there was a belief that there was a widespread shortage of psychiatrists, and that they were being rationed out to the regions. Miss PITT agreed that there was a shortage of consultant psychiatrists, and for that reason it was necessary to limit the posts in some areas. The numbers in post had increased between 1950 and 1960 in the Newcastle region by 33%.

Closure of Dispensary at St. Thomas's

Sir HUGH LINSTEAD (Putney, Con.) asked the Minister for a statement about the closing of the out-patient dispensary in the pharmaceutical department of St. Thomas's Hospital, London, because of the shortage of pharmacists on the staff. Mr. POWELL said he understood that difficulty arose because several of the dispensing staff left simultaneously, but he was asking the board to arrange for the dispensary to be reopened with as little delay as possible. He added that the number of hospital pharmacists had increased sharply in the last year or so. Experience elsewhere suggested that the difficulties which arose at St. Thomas's were quite exceptional. Mr. J. SNOW (Lichfield and Tamworth, Lab.) said there was a developing problem caused by the great demand in industry for qualified pharmacists. Mr. POWELL commented that industry was finding difficulty in getting all the people it needed.

Purchase of Unlicensed Drugs

Mr. K. ROBINSON asked the Minister why he had instructed hospital authorities to discontinue the purchase of all patented drugs from unlicensed sources, in view of the fact that he proposed to invite tenders centrally for only three groups of such drugs. Mr. POWELL told him that it was better that the procedure should be applied centrally. Dr. BARNETT STROSS (Stoke-on-Trent, Central, Lab.) said that this method would give justice to patent-holders, since it assured that they received their royalties, but asked why the Minister included in the first three groups hydrochlorothiazide, which had not yet been patented. Mr. POWELL told him this was because it belonged to the same group as another drug which it was desired to cover, and it was thought proper to call for tenders for both at the same time.

Reduction in Ionizing Radiations

Dr. BARNETT STROSS asked what was the average genetically significant dose of ionizing rays received by the population as a result of medical *x*-rays, giving the figure in terms of a percentage of the natural background radiation per generation of 30 years; and how this compared with the figure that could be achieved if all hospitals improved to the standard of the best hospitals. Mr. POWELL said it was estimated that in 1957 this was about 20% for all medical radiology, and that a reduction to 6% or less would be possible by improving techniques. Dr. STROSS called this a remarkable reduction, and asked what the Ministry were doing to make certain that every hospital followed the techniques in use at the best hospitals. Mr. POWELL recalled that when the Adrian Report was published he drew the attention of hospital authorities to the need to conform with the code of practice, and said that the code itself was being further improved in the light of the Adrian Report.

Universities and Colleges

UNIVERSITY OF LEEDS

On May 18 the honorary degree of D.Sc. was conferred on Sir Ronald Aylmer Fisher, Sc.D., LL.D., F.R.S., and Professor C. H. G. Macafee, F.R.C.S., F.R.C.S.I., F.R.C.O.G.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College held on May 27, with the President, Mr. Arthur C. H. Bell, in the chair, the gift of £5,000 from the Mathilda Kennedy Charitable Trust was gratefully acknowledged.

The following were elected to Council to fill statutory vacancies: *As Representatives of the Fellows:* London, Professor J. C. McClure Browne; England and Wales (excluding London), Mr. R. G. Maliphant and Mr. Robert Newton; Northern Ireland, Mr. Ninian McI. Falkiner; *As representatives of the Members:* London, Mr. E. A. J. Ament; Northern Ireland, Mr. G. B. Gibson.

The following were admitted to the Fellowship:

H. B. Bagshaw, D. Ballantine, S. J. Behrman, F. Benjamin, D. C. A. Bevis, Constance L. Beynon, J. M. Bowen, G. C. Brentnall, A. Broido, A. D. H. Browne, E. C. Bryant, A. D. Byrne, W. Calvert, Kate I. Campbell, L. A. Cruttenden, G. Dalley, J. Dei, N. E. C. de la Hunt, J. C. H. Dunlop, M. P. Embrey, I. B. Faris, H. D. Freeth, G. T. Gibson, J. H. Gibson, A. B. Hay, R. E. Hemsley, J. B. Hurll, R. G. Law, T. L. T. Lewis, Una G. Lister, W. J. McCord, W. G. MacGregor, Margaret A. Mackie, R. Murdoch, C. G. Paine, E. Parry-Jones, Peng Teik Por, Lilian Raferty, S. Ranjanayagam, W. D. Refshauge, K. S. Richardson, H. A Ripman, H. Roberts, C. G. Roworth Everall M. Shippam, W. R. Sloan, D. F. Smith, A. B. Stenhouse, P. C. Steptoe, Agnes M. Stewart, A. S. B. Studdy, G. S. Thomas, J. G. Thurston, E. Williams, E. A. Williams.

The following were admitted to the Membership:

A. G. Amias, Jean L. Baker, D. C. Beckingham, N. A. Beisher, F. R. Betheras. F. C. Bhattacharjya, Eunice R. Burton, Ramaswamy Chandravadhana, Sin Giap Chua, Evelyn Coates, Aileen F. Connon, K. Dar, D. A. Davey, C. S. Dawn, K. J. Dennis, P. L. C. Diggory, R. B. Dorofaeff, A. D. El-Tannir, J. A. L. F. E. Noel, C. W. Gale, A. Gillespie, H. Glietenberg, J. B. Gnanapragasam, Sek-Mun Goon, J. G. Griffiths, G. H. B. Hart, G. M. Johnstone, K. S. Karal, M. J. A. Kelly, W. A. Kirkpatrick, H. J. Kosasky, S. Kunstler, David Youn-Sen Liang, Ma Yin May, M. Mehra, Ma Khin Nu, U. N. Pathak, A. Penn, C. R. Porteous, Thelma Rasalam, Fay M. Rennie, W. J. St. N.-G. Rhys, A. Roy, Irene M. Salmon, Yvonne M. Salmon, J. I. Sanghvi, P. R. Sathyanadhan, E. Sayes, R. J. Seddon, N. K. Sen, P. C. S. Gupta, A. A.-el-F. Shandall, A. V. Shenoy, R. V. Stephenson, S. K. Suppal, Muriel M. H. Sutcliffe, T. C. Svensen, I. P. Thew, G. R. Thoms, V. R. Tindall.

The following candidates have been awarded the Diploma in Obstetrics:

A. Abdus-Salam, M. A. Aboud, A. H. Abrahams, Ada M. Adams, C. D. Addis-Jones, A. F. Adedoyin, S. K. Adhya, P. M. Aichroth, K. Amatayakul, I. F. Anderson, Elvira C. Arya, J. W. Aspinall, P. G. Atkinson, W. J. Atkinson, I. F. Ayad, G. Baker, S. Balakrishnan, R. Barker, Elizabeth M. Beattie, J. H. Bell, R. J. M. Bell, A. Bennett, J. W. Bennett, P. C. Bewes, T. A. Bhambhani, Joan Bishop, R. Y. Bishop, W. I. K. Bissett, R. C. Blake, J. W. Bland, A. R. Bowie, J. R. Bowles, Miriam J. B. Brady, Mary E. Braithwaite, E. C. Bramwell, H. Brenner, M. F. Brewster, A. Brickman. Helen B. Brodie, Dorothy A. Brown, J. S. Brown, W. F. Brown, M. Budd, A. E. Bullock, Maureen V. Burrage, Hazel M. Burtenshaw, R. M. Burton, M. Busson, Kathleen Calder, J. P. R. Campbell, R. M. Carr, A. F. Chalmers, D. K. Chaudhari, J. J. S. Chesser, J H. Cole, R. J. Cole, F. B. Coleman, Hellen S. Conn, B. J. E. Cooke, A. M. Cotton, W. G. R. Couldrick, D. D. Craig, J. C. Creedon, J. D. Crosbie, R. E. Cudmore, D. P. Cummine, R. L. C. Cumming, A. H. Davies, E. G. L. Davies, R. J. L. Davis, Gisele M. M. de Lane Lea, S. Dharmalingam, R. M. Din, Elizabeth C. Dobie, J. D. Donnelly, N. J. T. Donnelly, J. C. Doran, R. F. Dorrington, Allison C. Dunbar, A. Dunnill, M. K. Dunstan, C. Dunster, P. C. E. Edgecombe, T. G. Egan, F. R. Ellis, S. T. Eng, J. A. F. Evans, J. B. Evans, K. M. Evans, J. Fairley, Elizabeth A. Featherby, G. L. Featherstone, D. W. Ferguson, Dorothy J. O. Ffoulkes-Crabbe, R. M. Finch, Joyce Fleming, Lalita M. Fooks, A. L. Freeman, J. Fyfe, B. Gallagher, Louise Gallagher, G. R. Gerson, S. Ghosh, Vahine Gibbings, J. R. M. Gibson, R. Gillespie, E. W. Gillison, J. B. Glass, R. P. Golding, J. E. Goodess, K. J. Green, A. R. Grieve, Jane M. B. Griffiths, Margaret A. Griffiths, P. R. Grob, L. H. Grove, J. D. I. Hall, A. C. Halliwell, J. S. H. Hamilton, R. J. Hamilton, R. D. Harbinson, J. W. Harcup, A. W. Harcus, A. Harley, A. G. H. Heaney, J. D. Henderson, W. J. M. Hood, P. J. Hook, Maldwyn Hopkin-Thomas, R. G. Hornung, Helen M. Hoyle, J. D. W. Hunter, J. M. Hunter, R. J. Hunter, B. Igbogbahaka, E. H. Innes, J. J. B. Irvine, N. J. Jackson, Nesta B. James, G. H. C. Jenkins, A. C. Johansson, I. C. Johnson, G. D. Jones, Jane M. Jones, Modest C. Jones, Susan P. Jones, R. A. Jupe, B. Kamalamma, Loyola M. Kearney, A. G. Kerr, M. J. Kettle, F. F. P. Kierans, Shirley J. Knight, J. A. Kuzemko, Gwenda D. Larkin, B. H. Latimer, P. A. Lawrence, Barbara J. Ledsom, B. L. Lees, O. C. Legg, G. F. Lewis, T. S. Little, Cynthia Lucas, A. M. Lush, M. Lydon, W. McConnachie, I. A MacFarquhar, A. J. Mackintosh, W. D. Mackay, K. S. A. Madgwick, F. Mansfield, R. Marks, N. C. Marshall, Sheila C. Martin, Ann R. Matthews, A. J. Membrey, R. B. Miller, M. R. R. Moore, D. L. Morrison. R. Moulton, Philippa N. Mourant, Gillian K. Mucklow, F. H. Muir, J. S. Munro, P. J. Murphy, A. I. S. Murray, I. M. Murray, Mary A. Murray, Soe Myint, J. A. Naqshbandi, J. J. Nattrass, C. H. Naylor, Khin Khin Ne, B. T. J. Newland, J. C. Nicholson, J. L. Nimmo, Khin Khin Nu, C. F. O'Connor, E. L. Offerman, G. F. R. Ogilvie, C. J. M. O'Keeffe, R. Omar, Lilian L. Orba, B. W. G. Orr, J. T. Outred, H. R. Owadally, R. K. H. Parker, W. F. Parrott, H. M. Patel, Lalita A. Patel, Usha T. Patel, J. F. Patrick, Christine M. Peacock, P. E. Pearce, G. N. Penlington, C. R. Phillips, Eileen B. Phillips, R. W. Porter, M. Priest, L. W. Purnell, N. A. Purry, C. E. Puvimanasinghe, D. Ramprotal, S. A. Rance, R. Randall, S. V Rangwala, A. J. Reeves, T. J. Richards, C. J. Riley, M. E. Rivlin, N. A. Robinson, T. R. Robinson, B. K. Rogers, Jessie M. A. Rogerson, D. W. Ross, G. B. Ross, Elizabeth Rowe, G. C. Rowe, G. Rughani, P. Sadler, Phillida A. Sampson, D. N. Seaton, D. W. Seldon, K. T. Shah, S. G. Shaikh, E. Shaoul, Olive P. Sharp, A. G. Sherman, M. H. Shivdasani, N. L. Short, G. S. Shute, S. Siddiqi, M. W. Smillie, J. C. S. Smith, J. N. Smith, R. R. Smith, S. Spragge, Anne E. Staddon, D. M. Stainton-Ellis, J. F. Steele-Perkins, D. G. Strachan, D. J. Strath, M. J. Streule, I. T. Stuttaford, R. M. Swinburne, G. W. Tapper, A. R. Tappin, Margaret Taylor, C. Thomas, D. H. Thomas, W. Thomson, Jill M. Thwaites, R. E. Tonge, V. L. Tosh, J. E. C. Twentyman, B. C. Uzodike, Zarina I. R. Vellani, P. Vithiananthan, Anna G. Walker, I. W. Wallace, G. G. Ward, A. V. R. Watson, P. Watson, Margaret J. Watt, W. N. Waugh, J. N. Webb, W. White, A. Whitworth, Glenwynne Williams, J. B. Williams, C. J. F. Ll. Williamson, G. T. Wills, J. O. Woods, H. G. Wotherspoon, Heather E. Wright, Margaret E. G. Wright, J. D. Wyatt, R. J. Wylie, K. E. Young.

Vital Statistics

THE 1961 CENSUS

Preliminary results from the census held on April 23 were published last week by the Registrars-General of England and Wales[1] and of Scotland.[2] The following Table shows population changes since the previous census:

	1951	1961	% Change
England	41,159,213	43,430,972	+ 5·3
Wales	2,598,675	2,640,632	+ 1·6
Scotland	5,096,415	5,178,490	+ 1·6
N. Ireland	1,370,921	1,425,000*	+ 3·9
United Kingdom ..	50,225,224	52,719,604	+ 5·0
Isle of Man ..	55,253	48,151	−12·9
Jersey	57,310	57,200*	− 0·2
Guernsey and Associated Is. ..	45,496	47,198	+ 3·7
Irish Republic ..	2,960,593	2,834,000*	− 4·3

* Estimated figure.

England and Wales

The increase of 2.3 million for England and Wales is the largest ever recorded for a ten-year intercensal period. It is mainly due to a rise in the birth rate, but includes a net gain by migration from other countries (including Scotland) of 352,000. The increased flow of births dates from 1956–7, and is the result of marrying at an earlier age; consequently the higher birth rate may not be maintained if the average age at which people marry again becomes fairly stable. It is too early yet to say whether average size of family has increased.

For most of the ten years 1951–61 net migration was trivial in relation to natural increase, but in 1959 it accelerated greatly and in 1960–1 is estimated to have exceeded the excess of births over deaths.

The density of population in England and Wales is 790 persons per square mile (300 per sq. km.). Only one other major country in Europe is more crowded—the Netherlands with 893 per square mile (345 per sq. km.).

The population has increased most since 1951 in the counties of S.E. England, while in N. England and Cornwall it has increased least or in some areas declined. "The general picture is of a continued movement of industry to the south, or drift from the coalmining and textile areas of the north, growth of population in areas of the midlands where iron and steel, brickmaking, chemical industries are thriving, industrial expansion in southern areas with good communications with London or around south coast ports; a movement of dormitory areas further from the centre of conurbations, especially from London, as transport facilities have been extended by railway electrification schemes; and as an aspect of an ageing population a filling up of south-coast retirement areas." There is little change in the distribution of population between town and country from 1951 to 1961.

Females outnumber males, but for many years the difference has been shrinking. In 1931 there were 1,088 females per 1,000 males; in 1951, 1,082; and in 1961, 1,066. The counties of southern England were, in general, the places where females were in greatest excess (over 1,100 per 1,000 males), while in East Anglia and the S.E. Midlands the proportion of females was lowest (under 1,000 per 1,000 males).

Scotland

In contrast to England and Wales, Scotland had the lowest recorded increase in population since the 1921–31 interval.

[1] *Census 1961, England and Wales: Preliminary Report.* H.M.S.O. 7s. 6d net.
[2] *Preliminary Report on the Sixteenth Census of Scotland, 1961.* H.M.S.O. 5s. net.

The increase was 82,075 (1.6%), as compared with an increase of 5.2% from 1931 to 1951.

The loss by migration during 1951–61 was 254,701 persons. About half went to England and half overseas.

Of the 33 counties of Scotland, 15 show increases of population and 18 decreases. The largest increases were in Ayr, Dunbarton, Midlothian, Renfrew, and Fife, while the largest decreases were in Aberdeenshire, Bute, Argyll, and Banff. The population of Glasgow decreased by 3.2%, while increases were recorded for Edinburgh 0.3%, Aberdeen 1.4%, and Dundee 3.2%. In the crofting counties (N. and N.W.) the population decreased by 2.8%, and in the Border counties by 6.3%.

Females outnumbered males by 1,085 to 1,000. This is the same ratio as in 1931, but smaller than in 1951, when it was 1,094 to 1,000.

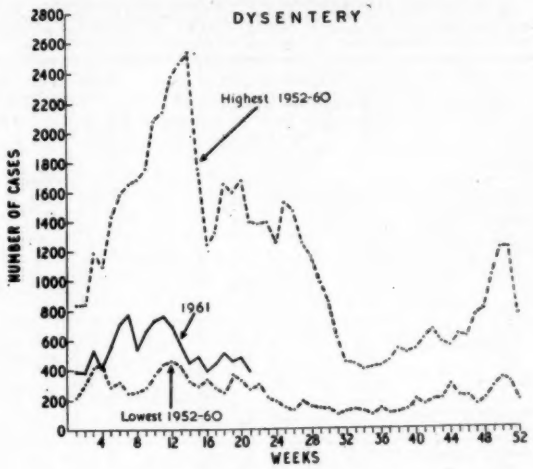
Infectious Diseases

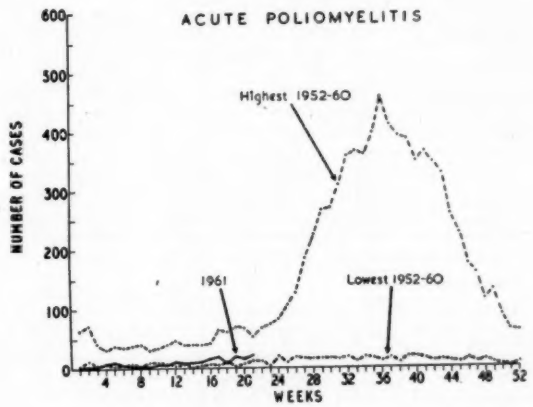
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

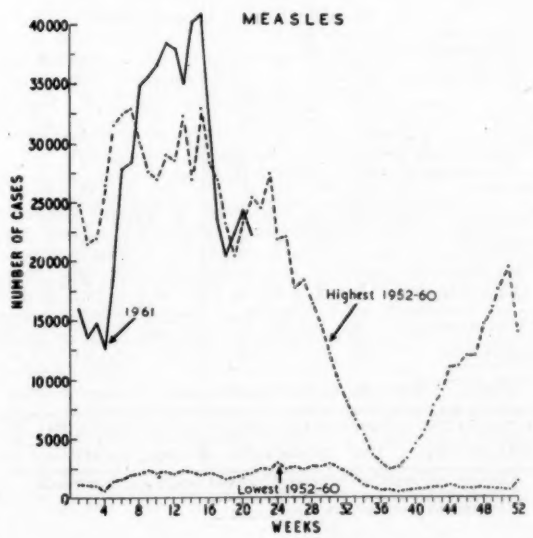
	Week Ending	
Measles	May 27	**June 3**
Devonshire	569	**679**
Plymouth C.B.	192	**318**
Gloucestershire	1,189	**1,089**
Bristol C.B.	546	**433**
Hampshire	673	**783**
Portsmouth C.B.	182	**155**
Lancashire	1,020	**1,126**
Liverpool C.B.	111	**161**
Manchester C.B.	116	**149**
Middlesex	1,113	**946**
Ealing M.B.	218	**192**
Northumberland	463	**667**
Newcastle upon Tyne C.B.	66	**252**
Nottinghamshire	210	**341**
Nottingham C.B.	43	**153**
Somersetshire	568	**619**
Bath C.B.	176	**186**
Staffordshire	1,459	**1,747**
Stoke-on-Trent C.B.	341	**511**
Surrey	894	**934**
Croydon C.B.	241	**157**
Sussex	597	**559**
Brighton C.B.	224	**212**
Warwickshire	658	**841**
Birmingham C.B.	298	**426**
Yorkshire West Riding	1,919	**2,174**
Leeds C.B.	247	**277**
Sheffield C.B.	314	**297**
Monmouthshire	417	**623**
Newport C.B.	156	**259**
Dysentery		
Essex	9	**28**
Epping and Ongar R.D.	0	**19**
Lancashire	96	**135**
Bolton C.B.	10	**14**
Liverpool C.B.	32	**30**
Manchester C.B.	10	**13**
Oldham C.B.	8	**16**
Urmston U.D.	3	**10**
Yorkshire West Riding	84	**61**
Leeds C.B.	20	**23**
Sheffield C.B.	3	**10**
Diphtheria		
London	4	**3**
Bermondsey	0	**2**

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 27** (No. 21) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	6	4	1		2	2	1	1	0	1
Dysentery	385	48	178	4	7	1,312	173	191	20	3
Encephalitis, acute	1	0		1		4	0	1	0	
Enteric fever:										
Typhoid ..	1	0	1	1		3	2	0	0	
Paratyphoid ..	5	0	0	0		3	1	0	0	
Food-poisoning ..	236	14	15	0		157	9	43	3	
Infective enteritis or diarrhoea under 2 years				10	25				22	27
Measles*	22,345	727	379	377	144	2,254	99	33	7	34
Meningococcal infection	17	0	11	3		25	3	8	0	2
Ophthalmia neonatorum	11	0	2	0		21	0	5	0	
Pneumonia† ..	213	14	147	5		256	17	185	7	5
Poliomyelitis, acute:										
Paralytic ..	9	0	0	} 0	3	{ 6	2	0	} 0	2
Non-paralytic ..	13	0	1			{ 6	2	0		
Puerperal fever§ ..	135	30	7	0	1	196	19	18	0	
Scarlet fever ..	384	19	41	13	13	606	35	56	9	12
Tuberculosis:										
Respiratory ..	364	48	63	18		459	66	76	23	
Non-respiratory	52	5	12	8		69	3	14	5	
Whooping-cough..	451	14	54	7	35	1,453	124	223	5	90

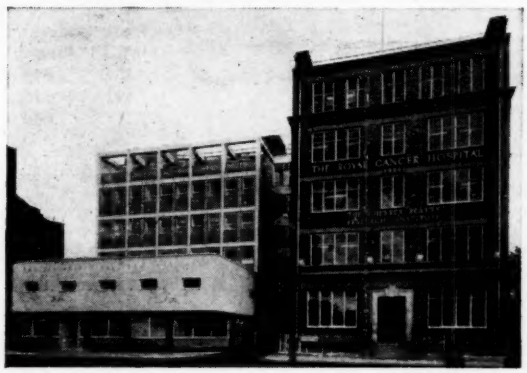
DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	1	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	0	1	0	8	0	5	0	0
Influenza	8		1	1	0	10	0	1	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia ..	437	45	22	16	1	480	41	15	9	3
Poliomyelitis, acute	4	0		0	0	0	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 61	{ 3	} 5	{ 1	6	} 68	{ 1	6	0	4
Non-respiratory		0		0	1		1	0	0	2
Whooping-cough..	1	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	284	30	35	6	4	349	35	30	6	10
Deaths (excluding stillbirths) ..	8,936	701	579	127	128	9,305	713	577	114	132
LIVE BIRTHS ..	14,283	1205	1139	262	374	15,793	1390	1055	308	380
STILLBIRTHS..	292	20	35			333	25	18		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Extension to Chester Beatty Research Institute Opened

The extension to the Chester Beatty Research Institute was opened on June 9—in the Institute's Jubilee year—by Sir HOWARD FLOREY, P.R.S. The new building, which lies alongside the old one, virtually doubles the space available to the Institute and was built at a gross cost of £300,000. The greater part of this sum was provided by the board of governors of the Royal Marsden Hospital from the trust fund which they hold in aid of the Institute. A grant of £40,000 from the Wellcome Trust has been acknowledged by the inclusion in the building of a Wellcome Laboratory of Pharmacology and Experimental Chemotherapy. Sir Howard, who was welcomed by Sir CHARLES DODDS, F.R.S., chairman of the committee of management, said



that work on the ultimate cause of the cellular changes in cancer demanded the use of all the most elaborate and refined physical and chemical techniques which have been introduced into biological studies during the last twenty or thirty years. "But," he continued, "how is work to be kept going in places such as this without putting what many senior scientists believe to be too crushing a burden on those responsible for scientific work by saddling them with the necessity first of all to collect the money to do it with?" In passing the vote of thanks, Professor A. HADDOW, F.R.S., the Institute's director, thanked those who had made the building possible, and acknowledged the financial support of the Medical Research Council, the British Empire Cancer Campaign, the United States Public Health Service, and various private American funds. He described the purpose of the new extension as the bringing to bear of the relevant disciplines upon problems of carcinogenesis, the special properties of the cancer cell, tumour immunology, virology, and chemotherapy; promoting the expansion of biological science; enabling them to plan ahead over the next ten years; and, not least, providing for an increasing host of visiting workers from the world over.

The new extension, which is shown here, has five floors and a basement housing the services, boilers, and a large assembly room seating 200 people. On the ground floor are the stores, the administrative rooms, and the photographic section. The first floor houses the physical chemistry laboratories and the clinical chemotherapy unit; the second the electron microscopy group, the tissue culture department, and some organic chemistry laboratories; space for the normal complement of 10 to 12 visiting workers and Professor Haddow's department are on the third floor. On the fourth floor are the departments of pharmacology and immunology, which are housed in the Wellcome laboratories, and on the fifth floor the animal houses. The third, fourth, and fifth floors are connected to the old building by flying bridges. (Architects: Messrs. Lanchester and Lodge (Mr. N. S. Morris).)

First Sir Ernest Kennaway Memorial Lecture

The first Sir Ernest Kennaway Memorial Lecture was delivered on June 12 by Professor ANTOINE LACASSAGNE, former director of the Institut du Radium (Institut Pasteur) and honorary professor of the Collège de France, in the conference room of the Chester Beatty Research Institute. Professor Lacassagne, who gave part of his lecture in French, told how he first met Kennaway in 1923 at what was then the Cancer Hospital in Fulham Road, and heard for the first time of his work on the carcinogenic properties of tar, work that was to pave the way to the understanding of industrial cancers. Kennaway's patient and systematic researches enabled workers at the Cancer Hospital to write in the course of a few years one of the most brilliant pages in scientific history. After tracing the developments that had followed in cancer research, Professor Lacassagne concluded by saying that, after half a century of research, we were only at the beginning of understanding the problem. Nevertheless, even in the present era of research on the role of viruses, one could say that what was most thoroughly understood and most solidly established in this difficult field still seemed to be the results furnished by the study of chemical carcinogenesis. These results were a witness to Kennaway's quality and to the immortality of his work.

College of G.P.s' Research Foundation

The College of General Practitioners has established a research foundation to promote and assist research by general practitioners in Great Britain and in the Commonwealth where faculties of the College exist. Initially, the income from £100,000 will be available. This represents about a third of the amount received for the £1m. appeal launched last year to provide the College with new headquarters, and for education and research. (See *Journal* annotation, March 5, 1960, p. 716.) The research projects on which the money will be spent will be approved and supervised by the College's research committee under the chairmanship of Dr. R. J. F. H. PINSENT; they may sometimes be undertaken by general practitioners who are not members of the College.

Safety Belt Anchorages for B.M.C. Cars

The British Motor Corporation has announced that all its cars are to be fitted with anchorages for safety belts. The anchorage points have been designed in consultation with Mr. W. GISSANE, clinical director, Birmingham Accident Hospital, and a firm of safety harness manufacturers.

N.A.M.H. Guide to Mental Health Act

The National Association for Mental Health has issued *The N.A.M.H. Guide to the Mental Health Act, 1959*. It contains an outline of the Act's main provisions as a guide to social workers and members of hospital and local authority committees, and indicates the changes brought about and the new machinery through which they will operate. (Price 2s. 6d. from N.A.M.H., 39 Queen Anne Street, London W.1.)

Amendments to Adoption Regulations

The new Adoption Agencies Regulations, 1961, make clear that it is open to registered adoption societies or local authorities to place a child with prospective adopters before the age of 6 weeks, and, therefore, before the test for syphilis or examination for phenylpyruvic acid have been carried out. The new provisions require that the test or examination shall be made as soon as practicable after the child has been placed and attains the age of 6 weeks. Where the examination for phenylpyruvic acid is concerned it is required only if the child is less than 2 years old, and, if required, must be made after the child is 6 weeks old.

Eleanor Roosevelt International Cancer Fellowships

The International Union Against Cancer, through funds made available by the Eleanor Roosevelt Cancer Foundation, will award annually fellowships for research on cancer. These are senior postdoctoral awards designed for the support of persons who, as full-time members of the staff of universities, teaching hospitals, research laboratories or other institutions, have demonstrated outstanding ability or promise as independent investigators in the field of research on the experimental and clinical aspects of cancer and who wish to broaden their experience by a period of study in another country. Details and application forms may be obtained from International Union Against Cancer, P.O. Box 400, Geneva 2, Switzerland.

International Children's Centre

Details of the annual Guigoz Fellowship and the Nestlé Fellowship, both for research on nutrition, may be obtained from the Public Relations Service, Château de Longchamp, Bois de Boulogne, Paris 16, France.

"British Medical Students' Journal"

Sixteen weeks in America at the expense of a Boston millionaire, an expedition to Russia, and hitchhiking to the Arctic are all described in the summer issue of the *B.M.S.J.* There are also articles on "A Thousand Years of Leprosy in Scandinavia," "The Royal Gift of Healing," and "Ambroise Paré—the Man: the Life of a Sixteenth Century Army Surgeon." Contributions for the next issue should reach B.M.S.A., B.M.A. House, Tavistock Square, London W.C.1, by August 14.

Professor Leiper's Festschrift

The issue of a special volume, or *Festschrift*, of the *Journal of Helminthology* in honour of Professor R. T. LEIPER, F.R.S., on the occasion of his 80th birthday, was noted in the *B.M.J.*, April 22, p. 1184. Copies of this birthday volume, running to 230 pages, can now be obtained (price 30s.) from Mrs. V. C. DAY, Winches Farm, Hatfield Road, St. Albans, Hertfordshire.

Salk Vaccine Inquiry in Australia

The Australian Government has set up a committee to inquire into problems encountered recently in the production of Salk anti-polio vaccine at the Federal Serum Laboratories in Melbourne. In the last six months two batches of the vaccine have failed to satisfy tests. Last month Australia began importing supplies of poliomyelitis vaccine from Canada because of the local production difficulties. The committee of inquiry will include Sir MACFARLANE BURNET.

Hospital Building Notes

Guidance on the design of radiological departments is given in Ministry of Health Hospital Building Note No. 6, *Diagnostic X-ray Department*, published by H.M.S.O. (price 1s. 6d. net). Note No. 2, *The Cost of Hospital Buildings*, has also been published by H.M.S.O., price 4s. net.

Ileostomy Association of Great Britain

The North-western Division of the Ileostomy Association was formed on May 6 under the presidency of Mr. A. R. ANSCOMBE. The secretary is Mr. A. CRESSWELL, 15 Risley Avenue, Harpurhey, Manchester 9.

Change of Title

The *International Journal of Air Pollution* has become the *International Journal of Air and Water Pollution*.

Pakistan's Increase in Population

A revision of Pakistan's second five-year plan has become necessary because provisional results of the 1961 census show that the population has already increased to 93.8 million. The plan assumed that by 1965 when the period ended the population would number 95 million. The figure is now more likely to exceed 100 million.

In Brief

Dr. M. G. CANDAU has informed the World Health Organization that there are now 481 doctors working in the Congo (Leopoldville) compared with the 761 employed there before independence was achieved.

The National Board of Family Planning has recommended to the Pakistan Government that, with certain provisos, a

bonus of 25 rupees should be paid to every male who is sterilized in the interests of family planning.

The directorate of religious affairs in Ankara has issued an official pronouncement that the practice of birth control by contraceptives—hitherto discouraged by some Muslim theologians—is permissible for Muslims.

The second midwives' training school to be opened in Uganda in two months has been opened at the Freda Carr Hospital, Ngora, in Teso District. It has been financed by a grant from the Uganda Government and a loan from the Church Missionary Society.

People in the News

Professor A. HADDOW, F.R.S., was one of the seven non-Russian scientists who were elected to membership of the Soviet Academy of Medical Sciences at its recent general meeting. Also elected were Dr. P. DUDLEY WHITE, the Academy's first American member, and Dr. V. R. KHANOLKAR, vice-chancellor of the University of Bombay.

Sir ROBERT PLATT, P.R.C.P., who gave the 1961 Lilly Lecture at the American College of Physicians' meeting in Miami, Florida, was made an Honorary Fellow of the College at the same meeting.

Sir ARTHUR PORRITT, P.R.C.S., is to be awarded an Honorary Fellowship of the American College of Surgeons at the A.C.S.'s annual clinical congress in October.

Dr. T. D. DAY, assistant director of cancer research, University of Leeds, has been appointed director of the Tobacco Manufacturers' Standing Committee Research Unit, Harrogate.

Mr. H. S. GRAINGER, chief pharmacist at Westminster Hospital, has been elected president of the Pharmaceutical Society.

COMING EVENTS

Biochemical Society.—Meeting, Department of Physiology and Biochemistry, University of St. Andrews: June 22, 2 p.m., colloquium, "The Quantitative Estimation of Amino-acids"; June 23, 10 a.m., original communications.

National Physical Laboratory, National Engineering Laboratory, and Building Research Station.—Conference, "The Control of Noise," June 26–28, National Physical Laboratory, Teddington, Middlesex. Details from Mr. D. W. ROBINSON, at that address.

Bone and Tooth Society.—Annual general meeting, June 28, 4.15 p.m., 234 Great Portland Street, London W.1.

8th Congress of European Organization for Research on Fluorine and Dental Caries Prevention (ORCA).—London, July 4–7, Royal College of Surgeons. Main themes: (1) "The Biochemistry of Normal and Carious Enamel" (chairman, Professor A. I. DARLING); (2) "Dental Epidemiology" (chairman, Professor G. L. SLACK). Details from Mr. P. M. C. JAMES, Royal Dental Hospital, Leicester Square, London W.C.2.

Medical Association for the Prevention of War.—Conference, "Pathogenesis of War," July 14–16, Newnham College, Cambridge. President: Prof. A. HADDOW, F.R.S. Details from the secretary, Dr. DOROTHY ARNING, 127 King Henry's Road, London N.W.3.

Royal Medical Foundation of Epsom College.—Annual general meeting of governors, July 19, 3.30 p.m., Medical Defence Union's Council Room, B.M.A. House, Tavistock Square, London W.C.1.

American College of Surgeons.—Annual clinical congress, Chicago, October 2–6. Details from Mr. R. S. MYERS, Public Relations Department, American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois, U.S.A.

4th National Turkish Congress of Ophthalmology.—Izmir-Turkey, September 13–15. Details from Professor Dr. SELAHATTIN ERBAKAN, Devlet Hastanesi, Izmir-Turkey.

8th International Cancer Congress.—Moscow, July 23–28, 1962. Details from Professor L. SHABAD, 14 Solyanka, Moscow, U.S.S.R.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 19

INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, 5 p.m., Mr. R. E. Ellis: Radiation Hazards and Protection (II).

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Brian Ackner: Neuropsychiatric Aspects of Acute Intermittent Porphyria.

Tuesday, June 20

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Ernestine Henry Lecture by Dr. J. M. Barnes: Mode of Action of Some Toxic Substances—With Special Reference to the Effects of Prolonged Exposure.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Mr. Aleck Bourne: Chronic Pelvic Woman.

Wednesday, June 21

BROOK GENERAL HOSPITAL, Shooters Hill, London S.E.—5.45 p.m., clinico-pathological conference.

●INSTITUTE OF CHILD HEALTH.—At Hospital for Sick Children, 5 p.m., Alex Simpson Smith Lecture for 1961 by Miss Isabella Forshall: Duplications of the Digestive Tract.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. K. V. Sanderson: Inflammatory Reactions in the Skin.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. S. Plummer: Thoracic Actinomycosis and its Treatment.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. D. Tyrrell: Some Recent Experiments on the Common Cold Problems.

Thursday, June 22

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Primary Skin Cancer.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professor J. E. Bordley (Baltimore, U.S.A.): Cochlear Potentials in Man.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—5 p.m., visit to Chelsea Physic Garden, Swan Walk, S.W.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. A. E. A. Read: Some Hepatic Problems.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.

ST. MARY'S HOSPITAL MEDICAL SCHOOL: DEPARTMENT OF PHARMACOLOGY.—At Lecture Theatre, Wright-Fleming Institute, St. Mary's Hospital, W., 5.30 p.m., Sir Halley Stewart Trust Lecture by Dr. R. A. Butler: Some Problems of the Pharmaco-kinetics of Anaesthetics.

WEST LONDON HOSPITAL MEDICAL SCHOOL.—At Nurses' Hall, 4.30 for 5 p.m., 14th Alex Simpson Smith Lecture by Professor A. J. Harding Rains: Researches Concerning the Formation of Gallstones.

Friday, June 23

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald: clinical demonstration.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. J. T. Chesterman: Some Aspects of Achalasia Cardiae.

ROYAL SOCIETY OF HEALTH.—At Town Hall, Stamford, 10 a.m., symposium: Welfare of Elderly Persons. (*a*) Dr. H. Ellis Smith: Growing Old—Who Cares?; (*b*) Mr. L. J. Roll, A.R.S.H.: Housing for the Aged; (*c*) Dr. P. E. Jackson: Evolution of a Geriatric Unit.

Saturday, June 24

●ASSOCIATION OF PSYCHIATRIC SOCIAL WORKERS.—At Cowdray Hall, Henrietta Place, London W., 3 p.m., general meeting. Presidential Address by Rt. Hon. The Earl of Feversham, J.P.: Changing Pattern of Mental Health Services.

NORTH-EAST METROPOLITAN THORACIC SOCIETY.—At London Chest Hospital, general meeting, 9.30 a.m., Dr. J. Smart and Dr. L. Capel: Problems in the Control and Organization of a Respiratory Failure Unit; 10.45 a.m., Dr. J. N. Pattinson: Vascular Abnormalities of the Lungs; 11.45 a.m., Mr. J. R. Belcher: Surgical Treatment of Asthma; 2 p.m., discussion of Problem Cases.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Williams.—On May 30, 1961, at Edgbaston, Birmingham, to Enid, wife of Dr. R. Fraser Williams, a brother and a sister for Gweno and John—Adrian Fraser and Ruth Hilary.

DEATHS

Anderson.—On May 24, 1961, at Scio House, Putney, London S.W., Henry Stewart Anderson, C.M.G., L.R.C.P.&S.Ed., L.R.F.P.S., Lieutenant-Colonel, R.A.M.C., retired, aged 89.

Boag.—On May 29, 1961, at 12 The Drive, West Wickham, Kent, John Hamilton Boag, M.B., Ch.B., D.P.H., aged 72.

Craig.—On May 26, 1961, at Lichfield, Staffs, Alexander Henderson Craig, M.B., Ch.B., Brigadier, I.M.S., retired, of The Coach House, Elvetham Road, Fleet, Hants.

Hamilton-Pearson.—On May 23, 1961, at Alderney, Edgar Alan Hamilton-Pearson, M.B., Ch.B.

Hirst.—On May 27, 1961, in hospital, Joseph Walker Hirst, O.B.E., T.D., M.R.C.S., L.R.C.P., Hon. Colonel, R.A.M.C., of Delamere, Fixby Road, Huddersfield Yorks.

Hutchison.—On May 29, 1961, in a nursing-home, Bournemouth, Hants, Cyril Bertram Hutchison, M.R.C.S., L.R.C.P., late of Deal, Kent.

Khin.—On May 31, 1961, at the Kent and Sussex Hospital, Tunbridge Wells, Kent, Henry Aung Khin, M.B., F.R.C.S.Ed., Lieutenant-Colonel, I.M.S., retired, of 20 Chancellor House, Tunbridge Wells.

Nairn.—On June 1, 1961, at his home, 84 Harley Street, London W., Charles Godfree Nairn, M.B., F.R.C.S.Ed., M.R.C.O.G., aged 46.

Shann.—On May 27, 1961, at 81 Kennington Road, Kennington, near Oxford, Gerald Davenant Shann, M.R.C.S., L.R.C.P., D.P.H., aged 72.

Shortt.—On May 24, 1961, at his home, 1 Orchard Rise, Kingston-upon-Thames, Surrey, Cecil de Lisle Shortt, M.D.

Smeall.—On May 26, 1961, at 5 Nile Grove, Edinburgh, John Telfer Smeall, *M.C.*, M.B., Ch.B., D.P.H., aged 85.

Todd.—On April 25, 1961, at his home, 53 York Avenue, East Sheen, London S.W., Edward Finlay Ross Todd, M.B., Ch.B., aged 44.

Walker.—On May 25, 1961, at Woodthorpe, Padiham, Lancs, Allan Walker, M.B., B.S.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Blood Counts During Chlorpromazine Treatment

Q.—*Should blood counts be done from time to time in patients who are on continuous chlorpromazine treatment for mental disorder?*

A.—Phenothiazine derivatives such as chlorpromazine and promazine can cause blood dyscrasias. In a recent paper Korst[1] reviewed 71 cases of agranulocytosis, 59 of which were attributed to chlorpromazine and 12 to promazine. The majority of the patients were being treated for mental disorder, and in two-thirds of the cases the blood dyscrasia developed within 76 days of starting treatment. The amount of the drug which had been given before the onset of agranulocytosis varied from 1 to 52 g., with a mean of 12.3 g. Korst estimates that the incidence of this toxic effect may be as high as 3 per 1,000 patients treated. There is no doubt, therefore, that there is a risk of agranulocytosis in patients who are on continuous chlorpromazine treatment for mental disorders, and that this risk is greatest during the first three months of treatment.

Whether the performance of frequent blood counts in such patients does anything to minimize this risk is extremely doubtful. There is no doubt that many drugs which cause agranulocytosis may produce a leucopenia within a few weeks or months of starting treatment, but this does not necessarily herald the onset of agranulocytosis. Most often the depression of the white-cell count is transient, and even if the drug is continued the count will rise again.[2] Referring to another drug which can cause agranulocytosis, thiouracil, Himsworth[3] expressed the opinion that frequent white-cell counts were worse than useless as a precaution against the development of agranulocytosis. "Useless because agranulocytosis develops like a bolt from the blue and sometimes within two to three days of a normal blood count; worse than useless because a normal blood count may impart a quite unjustifiable sense of security." The only real safeguard against the dangers of agranulocytosis is to be aware of the hazard, and, especially during the critical period from three weeks to three months from the onset of treatment, to regard any complaint of fever or sore throat seriously and make a blood film immediately. If no granulocytes are seen in the film, then intensive treatment with penicillin and perhaps corticosteroids should be started at once.

REFERENCES

1 Korst, D. R., *J. Amer. med. Ass.*, 1959, **170**, 2076.
2 Wintrobe, M. M., *Clinical Hematology*, 4th edition, 1956. Kimpton, London.
3 Himsworth, H. P., *Brit. med. J.*, 1948, **2**, 61.

Bleeding for Haemochromatosis

Q.—*I have a patient with haemochromatosis. He is a moderately severe diabetic, and has a very large liver. Would you advise bleeding? If so, how much, how often, and for how long? If improvement does in fact take place, what objective indications would there be of this?*

A.—Venesection is the only treatment likely to be effective. It should be carried out at weekly intervals, 500 ml. of blood being removed at a time. There may be an initial fall in haemoglobin, which should not be allowed to drop below 11 g. per 100 ml., but after a few weeks this is compensated for by increased erythropoiesis. Weekly venesection should be continued for 18 months to two years, followed by bleeding every two to three months.

There is often a well-marked initial improvement in general well-being. A decrease in liver size and improvement in glucose tolerance may be expected as objective evidence of response to treatment in the present case. Improvement has also been reported in cardiac, thyroid, anterior pituitary, and gonadal function when these organs are involved.

A valuable account of this type of therapy has been given by McAllen, Coghill, and Lubran.[1]

REFERENCE

1 McAllen, P. M., Coghill, N. F., and Lubran, M., *Quart. J. Med.*, 1957, **26**, 251.

Expression of Haemoglobin Values

Q.—*What is the accepted standard for expressing haemoglobin values? Expression in percentage seems to be the least confusing (taking 100% as normal), since it gives a rough idea of the amount present in an individual.*

A.—The difficulty in expressing haemoglobin values in percentages of normal is that different workers consider different levels as 100% normal. The first 100% scale was devised by J. S. Haldane and corresponds to 13.8 g. of haemoglobin per 100 ml. of blood. The average normal value was based on the level in four individuals. Another widely accepted 100% scale is that of Sahli, where the 100% value amounted originally to 17.3 g. per 100 ml., but was later on lowered by the manufacturers who produced the Sahli apparatus for measurement of haemoglobin. Another by Dare considers 16 g.% as 100% normal. This confusion alone would justify the transition to an accurate expression in grammes per cent. There is, however, yet another argument. The normal haemoglobin level differs in men and women, and what might be a 100% normal in men may be more than 100% normal in women. It is now generally agreed to consider the average haemoglobin content of normal blood as either 14 or 14.5 g.%. The most recent British Standard specification puts the 100% level at 14.6 g.%; this corresponds to 105% on the Haldane scale and 85% on the Sahli scale. Taking the normal value for men at 15.6 g.% and for women at 13.7 g.% according to the Haldane scale the normal value would be 113% for men and 89% for women.

Testing for Colour Blindness

Q.—*What is the best and most reliable simple method for testing for colour blindness in the surgery?*

A.—Undoubtedly the most reliable method is by using the Ishihara isochromatic plates, obtainable as *Tests for Colour Blindness*, by S. Ishihara, and published in London by H. K. Lewis.

Pseudoxanthoma Elasticum

Q.—*What is the treatment for pseudoxanthoma elasticum?*

A.—In pseudoxanthoma elasticum the elastic fibres show degenerative changes which are not confined to the skin but which also account for the presence of angioid streaks seen in the retina. The elastic tissue of blood-vessels is similarly involved. This disorder is inherited as a recessive trait and seems to affect females predominantly. There is unfortunately no effective treatment.

Oxygen Content of Mixture from Minnitt Machine

Q.—*In the obstetrical department of the hospital in Canada where I work we have, for general use, a Minnitt gas-and-air machine, which was introduced by an obstetrician recently returned from England. Because of the low oxygen percentage (10%, I understand) delivered by this machine, I question the advisability of its use, especially in obstetrics. I would be grateful for your opinion.*

A.—It has been proved in practice, times without number, that the Minnitt gas-and-air apparatus, introduced in October, 1933, for the relief of the pains of labour, is perfectly safe for both mother and child. It was devised only to administer analgesia and not anaesthesia. When

it comes to discussing the low oxygen content of the mixture delivered by the machine the following points must be remembered.

(1) The figure of approximately 10% oxygen was an estimate made from an experiment on the bench, where a constant flow of the mixture was drawn mechanically from the apparatus.

(2) Administration is intermittent and respiratory effort irregular when the machine is in use in the labour ward, therefore the gas-and-air mixture may be different. That this is so is suggested by the fact that patients do not become cyanosed during the administration of nitrous oxide and air by this technique.

(3) The following is an account of an estimation of the oxygen saturation of the haemoglobin in the arterial blood in two subjects inhaling from the apparatus compared with a control.

	Subject 1 Percentage O_2 saturation	*Subject 2* Percentage O_2 saturation
The control	91	98
After inhaling from the apparatus for three minutes	93	91
Voluntary hyperventilation from the apparatus ..	93	86

These observations confirm the advisability of the employment of this method of gas-and-air administration in midwifery, but it should be used only in normal labour.

Transverse Furrowing of Nails

Q.—*Is there any medical significance in on-and-off transverse furrowing of the nails of practically all fingers of both hands? Excluding a local cause, does it point to any illness in the past or present (blood or nutritional disorder)?*

A.—This type of transverse furrowing of the nails can very often be traced to some upset of the general health. One should, of course, observe that the part of the nail thus affected is the matrix, which lies proximal to the visible nail. About six weeks has probably elapsed since the illness which produced the furrow by the time that it actually appears on the visible nail. The type of disorder most likely to produce this type of dystrophy is, I think, an acute febrile illness rather than a blood or nutritional disorder.

Hyaline Membrane

Q.—*A patient of mine has had two babies within the last 12 months, both born prematurely at about 32 to 34 weeks, and both have died within a short time. The post-mortem report has been asphyxia due to hyaline membrane. What is this condition?*

A.—Hyaline membrane is a condition that affects the lungs of newborn infants, especially though not exclusively the premature. Caesarean section and maternal diabetes are recognized predisposing factors, but very many cases occur in the absence of these. A layer of solid, amorphous (" hyaline ") material forms on the surface of the bronchioles and infundibula, and is associated with severe resorption atelectasis of intervening alveolar tissue. This is one of the commonest pathological conditions found at necropsy in premature newborn infants.

The composition of the membrane and the cause of its formation are not certainly known. Formerly it was believed to be composed of vernix caseosa inhaled from the amniotic sac by an anoxic foetus.[1] This theory has now been discarded by most authorities, but opinion is still divided between the blood[2] and the bronchial mucosa[3,4] as the source of the hyaline material. Some observers have sought to incriminate oxygen,[5] but the evidence is inconclusive.

The condition comes on during the first few hours after birth. It is not found in stillborn foetuses. In fatal cases death ensues usually between 2 or 3 and 72 hours after birth, most often during the first or second day. The diagnosis can be made during life with a fair degree of accuracy. The infants may be in poor shape at birth or may appear well at first. After a few hours they develop respiratory difficulty with cyanotic attacks, increasing in severity until death. There is, however, clinical and radiological evidence[6] that some affected infants recover, but the mortality is high.

REFERENCES

1 Farber, S., and Sweet, L. K., *Amer. J. Dis. Child.*, 1931, **42**, 1372.
2 Gitlin, D., and Craig, J. M., *Pediatrics*, 1956, **17**, 64.
3 Tregillus, J., *J. Obstet. Gynaec. Brit. Emp.*, 1951, **58**, 406.
4 Lynch, M. J., and Mellor, L. D., *Lancet*, 1955, **1**, 1002.
5 Bruns, P. D., and Shields, L. V., *Amer. J. Obstet. Gynec.*, 1951, **61**, 953.
6 Donald, I., and Steiner, R. E., *Lancet*, 1953, **2**, 846.

NOTES AND COMMENTS

Antidiabetic Drugs in Disseminated Sclerosis.—Dr. R. S. HOLZER (Birmingham) writes: You have recently published a question and answer about the value of antidiabetic drugs in disseminated sclerosis (April 29, p. 1268). After reading G. T. Sawyer's preliminary report referred to in your answer, I conducted a double-blind trial with tolbutamide in 11 patients (six women and five men) whose ages ranged from 32 to 50 years. None of the patients treated showed an improvement in any respect, which, because of the hope inspired by Dr. Sawyer's report, was disappointing. It may be said that my patients were all advanced cases needing hospital care and with insecure domestic backgrounds. There was some doubt about their ability or willingness to co-operate and the truthfulness of the statements made by them. I presume trials are in progress in other hospitals, and the results will be interesting.

OUR EXPERT replies: In my reply to the original question I pointed out that Sawyer's report was only a preliminary communication, and that, although his results were encouraging, the number of patients treated was small and that considerable confirmation of these results would be required before it could be concluded that oral antidiabetic drugs were of value in the treatment of multiple sclerosis. The results mentioned by Dr. Holzer and those of a larger and more comprehensive double-blind trial reported by Dr. Henry Miller and his colleagues from Newcastle[1] clearly have not confirmed the original findings, and it now seems certain that the sulphonylureas will share the fate of so many other drugs which, after an initial encouraging report, have been found to be ineffective in the treatment of multiple sclerosis.

REFERENCE

1 Foster, J. B., Miller, H., Newell, D. J., and Kinley, L. J., *Lancet*, 1961, **1**, 915.

Vaginitis in a Child.—Dr. B. K. H. NAIR (Brighton) writes: With regard to the treatment of vaginitis in childhood (" Any Questions? " May 13, p. 1405) I would like to point out that your expert has overlooked the fact that threadworms are often a predisposing, if not an exciting, cause of vaginitis in children. Threadworms setting up an irritation about the anus and causing scratching of the anus and vulva are often responsible for the spread of infection, and their presence tends to perpetuate the vaginitis. Eradication of threadworm infestation will help to clear up a vaginitis, especially those which relapse after treatment by the local and general measures mentioned in the answer.

Corrections.—Mr. A. P. Costain, Member of Parliament for Folkestone and Hythe, proposed the toast to the Harveian Society at the Buckston Browne/Gray Hill dinner held in the House of Commons on May 24, and not Sir Richard Costain as stated in the *Journal*, June 3, p. 1618.

We regret a misprint in Dr. J. Birch's letter on " Distasteful Advertising " (June 3, p. 1611). " The very frequent letter " should have read " The very infrequent letter."

Snake-bite antiserum: the telephone number of the Northampton General Hospital is now Northampton 34700.

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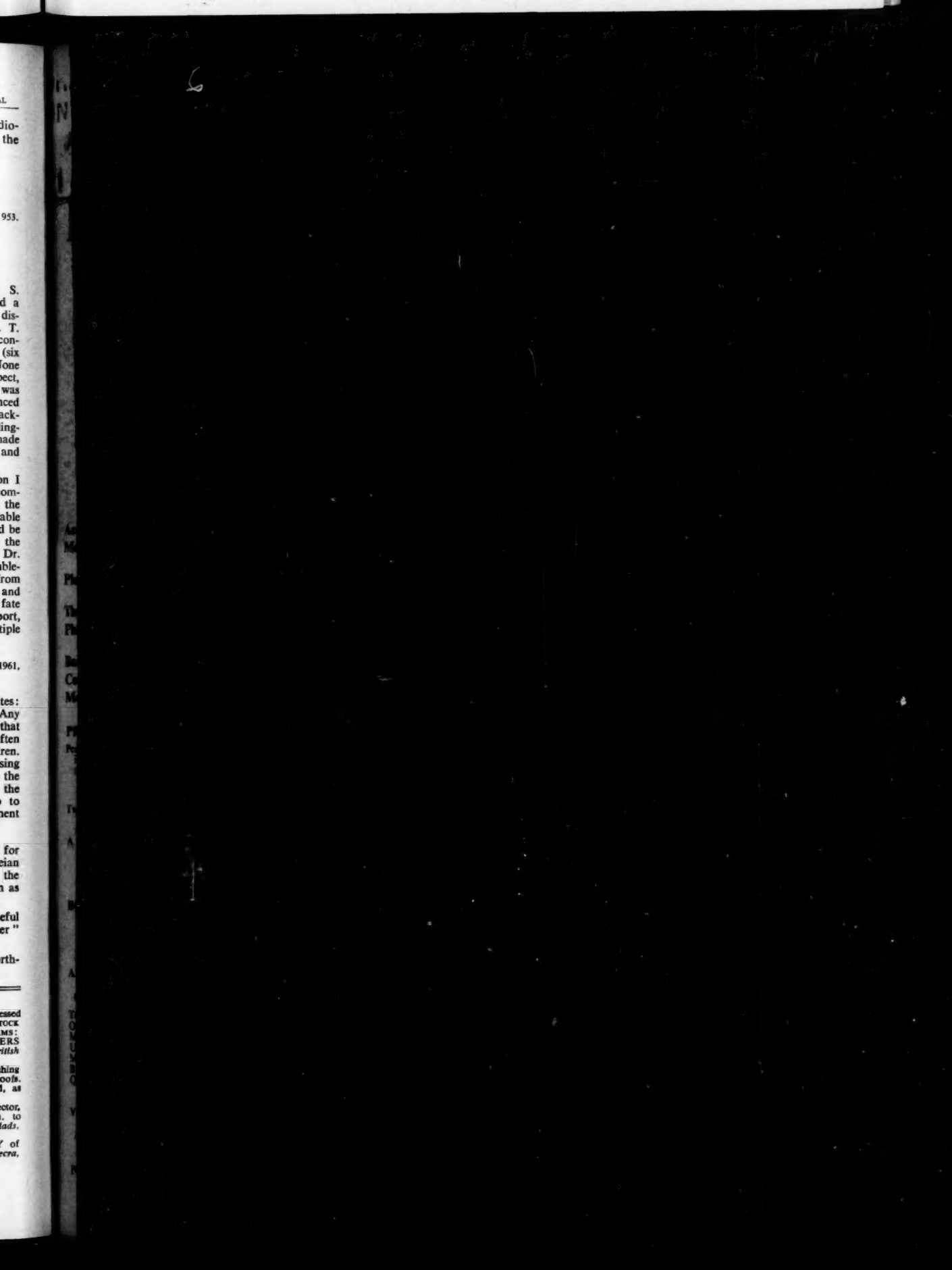
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